DISSERTATION ON

SERUM LIPOPROTEIN(a) [LP (a)] LEVELS IN YOUNG ISCHEMIC STROKE

SUBMITTED FOR

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CERTIFICATE

This is to certify that this dissertation entitled **"Lipoprotein(a) levels in young ischemic stroke"** submitted by **Dr. M.M.Kavitha** to the faculty of Internal Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D., degree Branch I (Internal Medicine) is a bonafide research work carried out by her under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Stroke is one of the most common causes of morbidity and mortality. It causes long-term disability to most of the patients[1]. Apart from the known risk factors like hypertension, diabetes and dyslipidemia newer risk factors like homocysteine, fibrinogen and **lipoprotein(a)** are emerging!

Lipoprotein(a) has been implicated recently to the occurrence of vascular events (coronary, cerebral and peripheral)[2]

Several case control and cross sectional studies have reported higher levels of **lipoprotein(a)** in stroke and transient ischemic attacks.[3-7]

Existing prospective trials have failed to demonstrate an association of **lipoprotein(a)** and the future risk of stroke. So the results are contradictory and it lacks consistency[8-13].

Indian studies relating **lipoprotein(a)** to stroke are lacking. Hence this study was conducted primarily to find out the **lipoprotein(a)** levels in young ischemic stroke and to analyse it.

AIMS OF THE STUDY

1. To study the levels of **lipoprotein(a)** in young ischemic stroke

   (40 years or less).

2. To assess whether **lipoprotein(a)** is an independent risk factor for ischemic stroke.

3. To compare levels of **lipoprotein(a)** between control and diseased.

4. To assess variation of **lipoprotein(a)** levels with age.

5. Correlation of **lipoprotein(a)** levels between men and women.

6. Relationship of **lipoprotein(a)** levels to recurrent ischemic stroke.

7. Comparison of our study results with other Indian and foreign study results.

EPIDEMIOLOGY OF STROKE

Stroke is a heterogenous syndrome caused by many disease mechanisms, all of which result in disruption of cerebral blood flow and subsequent tissue damage. It is the third leading cause of death and one of the commonest cause of disability in adults.[14]

In 2001, stroke accounted for 5.5 million deaths worldwide. It is equivalent to 9.6% of all death. Developing countries accounted for two- third of the deaths.

The average age of patients with stroke is 15 years younger in developing countries.[15]

The death rates due to stroke is higher in male than in female. But in population aged 65 years and over, when most strokes occur, the death rate in women outnumber men.

The reason for this apparent contradiction is that women outlive men and that age is an important risk factor for stroke[16]. [Department of Health and Human Services, national centre for health statistics].

The limited data available indicate that stroke occurring in young people is more often atherothrombotic in origin in developing countries, [17-19] in contrast to developed countries where arterial dissection and cardio embolic etiology predominate.[20-22]

Total stroke incidence rate increases exponentially with age for both men and women.

The prevalence rate for cerebrovascular diseases vary throughout the world from 1.43-20/1000. The highest rates were recorded in Japan (20/1000).

ASIAN PERSPECTIVE: CHANGING TRENDS

Earlier studies noted that Asians have a lower rate of coronary heart disease and higher prevalence of stroke.[23] Among the Asians, the death from stroke

outnumber that of coronary heart disease by three times. The age standardized, gender specific stroke mortality rate was 44 to 102.6/1,00,000 for Asian males, compared with only 19.3 for Australian white males.[23]

The disparity between stroke and coronary heart disease (CHD) incidence rates is usually attributed to high prevalence of hypertension and low levels of blood lipids among the Orientals. The above epidemiological data among Asians is based on the surveys carried out in Chinese population.

There is a shift in this trend for the past two decades. By 1985, coronary heart disease (CHD) became commoner than stroke as the cause of death among Japanese. This mortality profile parallels the change in the dietary habit. The current Japanese diet have increased animal fat and reduction in the amount of common salt.

INCIDENCE OF STROKE IN INDIA

Conducting an epidemiological survey in a developing populated country like India is a daunting task. According to the Asian Acute Stroke Advisory panel, India is still ranked among the countries where the information on stroke is minimal. The Global Burden of Disease study 1997, reported 9.4 million deaths in India, out of which 619,000 were from stroke. Disability adjusted life years (DALY) for stroke was calculated as 28.5 million. It was 6 times more than malaria[24].

Several population-based surveys on stroke were conducted from different parts of India, primarily to determine the cross sectional prevalence. [Reference, Table: A]

Very few surveys in India have determined the Annual Incidence Rate (AIR) of stroke. [Table: B]

All these surveys were underestimates because only the stroke survivors and not the stroke death cases were included.

Stroke related mortality is hugely under estimated because medical certification of cause of death is not followed. Only 13.5% of all deaths in India were medically certified[23] in 1994. It was estimated that stroke represented 1.2% of total deaths in the country, when all ages were included. The proportion of stroke death increased with age, and in the oldest group (of greater than 70 years of age) it represented 2.4% of all deaths.

According to the reports available, the prevalence rates of stroke for

North India (Kashmir) being 143/1,00,000

East India (Assam) 270/1,00,000

West India (Mumbai) 245/1,00,000

South India (Vellore) 64/1,00,000.

Average range being 90-220 /1, 00,000 persons. This report does not take Transient Ischemic Attacks (TIA'S) into account.

The Indian Collaborative Acute Stroke Study (ICASS) was a prospective multicentric study on unselected CT confirmed cases of acute stroke (less than 72hours) admitted to major university hospitals in India[24]. (Chandigarh, New Delhi, Mumbai, Pune, Bangalore, Chennai, Hyderabad.).

During the study period between 2002-2004, reliable information was collected in 2162 acute stroke cases. It was reported that the incidence of stroke was rising with advancing age – the maximum being in the age group of 41-70years. Ischemic strokes accounted for 77%, hemorrhagic strokes 22 % and unspecified account for 1 %.

RISK FACTORS FOR STROKE

MAJOR

- Hypertension
- Heart disease
- Cigarette smoking
- Transient ischemic attack.

SECONDARY

- Increased serum cholesterol/lipids

- Physical inactivity
- Obesity.

EVOLVING RISK FACTORS

- Lipoprotein(a)
- Apoprotein ‘E’ allele
- Serum homocysteine
- Factor 5 Leiden mutation.

LESS WELL DOCUMENTED

- Excessive alcohol intake
- Drug abuse
- Acute infections.

The single most important risk factor for stroke is **age of the individual** .Of all the controllable risk factors, hypertension is the most important [Wolf PA, et al, 1992]. Hypertension accelerates the atherothrombotic cerebral infarction. It also increases the risk of hemorrhage by promoting cerebral vascular microaneurysms. (Charcot Bouchard aneurysms). [Harrison’s Principles of Internal Medicine]

NON-MODIFIABLE RISK FACTORS IN STROKE

- Age
- Male sex
- Race
- Diabetes mellitus
- Prior stroke / Transient Ischemic Attacks
- Family history of stroke
- Asymptomatic carotid bruit.

MECHANISMS OF STROKE

Stroke is classified broadly into,

a) Ischemic stroke

b) Hemorrhagic stroke.

Ischemic stroke comprises 80% of the incident strokes and hemorrhagic stroke makes up the remaining 20%.

Ischemic strokes can be classified into,

1. Embolic stroke
2. Thrombotic stroke
3. Lacunar stroke
4. Watershed infarcts.

EMBOLIC STROKE

Embolic may be either cardiac or arterial in origin. Cardiac sources include atrial fibrillation, recent myocardial infarction, prosthetic valves, native valvular disease, endocarditis, mural thrombi, dilated cardiomyopathy or patent foramen ovale. Arterial sources are atherothrombotic or cholesterol emboli that develop in the arch of aorta and in extracranial arteries.

THROMBOTIC STROKES

Thrombotic stroke include,

a) Large vessel stroke

b) Small vessel (or) lacunar stroke.

They are due to insitu occlusions on atherosclerotic lesion in the carotid, vertebrobasilar and cerebral arteries.

Thrombogenic factors include,

a) Injury to and loss of endothelial cells. This exposes subendothelium resulting in platelet activation

b) Activation of the clotting cascade

c) Inhibition of fibrinolysis

d) Stasis of blood.

LACUNAR STROKE

Lacunar stroke represent 20% of all ischemic strokes. They occur when the penetrating branches of the middle cerebral artery, the lenticulostriate arteries, or the penetrating branches of the circle of Willis, vertebral artery or basilar artery become occluded.

Causes of lacunar infarcts are,

Microatheroma

Lipohyalinosis

Fibrinoid necrosis

Secondary to hypertension or vasculitis

Hyaline arteriosclerosis

Amyloid angiopathy.

WATERSHED INFARCTS

They are also called as border zone infarcts, develop from relative hypo - perfusion in the most distal arterial territories and produce bilateral symptoms. They occur in perioperative conditions or in situations of prolonged hypotension.

YOUNG STROKE

Though cerebral infarction is predominantly a disease of the senescence, its occurrence in younger age groups is not rare (Thorvalsden et al., 1995). Stroke in the young is particularly tragic because of the potential to create a long-term burden for the victims, their families and the community (You et al., 1997).

The hospital admission rates often vary from country to country. Regardless of the percentage of cases occurring among young individuals, most authors today agree

that among victims of cerebral infarction, young people are not rare (Bogousslavsky and Pierre 1992, Bevan et al., 1990 and Rouhaet et al., 1993).

The etiological investigations of young patients with cerebral infarction have identified a large number of possible causes (Bausal and Sood 1986, Biller et al., 1986 and Adams., et al., 1986). Inspite of extensive investigations, in 16 % of such patients a clear underlying cause is not found (Adams et al., 1995 and Neto et al., 1996).

The prevalence and risk factors involved in young stroke vary from the older individuals. 20-30 % of the hospital stroke populations fall below the age group of 40years.

In persons aged 20-44 years in a U.S study [1993-1997], the Annual Age-Adjusted Stroke Incidence Rate was 23 per 100,000 persons per year. [Stroke V: 33 12/02 P2789].

Ischemic stroke occurring in young Indians could well be a manifestation of accelerated cerebrovascular atherosclerosis. The traditional risk factors like hypertension, diabetes and smoking along with certain other evolving risk factors play a role in the pathogenesis of young ischemic stroke.

In 1996, Neto et al., studied the possible causes of cerebral infarction in patients aged fifteen to forty years.

They classified the patients into five subgroups namely,

1. Large artery atherosclerosis
2. Small vessel occlusion (or lacunes)
3. Cardioembolism
4. Stroke of other determined cause
5. Stroke of undetermined cause.

LARGE ARTERY ATHEROSCLEROSIS

In this group the recognised risk factors like,

1. Arterial hypertension
2. Smoking
3. Left ventricle hypertrophy
4. Heavy alcohol consumption
5. Hypercholesterolemia played the causative role.

According to investigators, the number of atherothrombotic infarctions is small among young patients (Alvarez et al., 1989 and Bogousslavsky and Pierre 1992).

SMALL VESSEL OCCLUSION

The risk factors for small vessel occlusion were,

1. Hypertension
2. Diabetes mellitus
3. Left ventricular hypertrophy.

CARDIOEMBOLISM

The source of embolism detected were,

1. Synthetic prosthesis
2. Mitral valve prolapse
3. Dilated cardiomyopathy
4. Apical aneurysm
5. Double mitral lesion
6. Segmental hypokinesia

7. Recent myocardial infarction

8. Aseptic endocarditis.

STROKE OF OTHER DETERMINED CAUSES

This group included more than 15 different causes of cerebral infarction. These cases include,

a) Protein C deficiency

b) Sickle cell anaemia

c) Protein S deficiency

d) Arterial dissection

e) Moya Moya syndrome

f) Vasculitis

g) Systemic lupus erythematous

h) Primary antiphospholipid syndrome

i) Migraine

j) Use of oral contraceptive pills.

The fifth group included patients in whom the etiology of cerebral infarction was undetermined despite an extensive workup.

Emerging risk factors like **lipoprotein(a)**, homocysteine and fibrinogen could constitute the fifth group. Other causes include Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke like Episodes (MELAS) and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarct and Leucoencephalopathy (CADASIL).

BIOLOGY OF LIPOPROTEIN(a)

Lipoprotein(a) was described by **Berg in 1963.**[25] The role of **lipoprotein(a)** gained clinical significance after 1987, when **Mclean et al,** suggested the structural homology between apoprotein(a) and plasminogen.[26]

STRUCTURE OF LIPOPROTEIN(a)

Lipoprotein(a) is a low density lipoprotein (LDL)) like molecule. It consists of apoprotein B-100 particle attached by a disulphide bridge to apoprotein (a).[27]

Apoprotein(a) is a member of a family of "**Kringle**", containing proteins such as plasminogen, tissue Plasminogen Activator (**tPA)**, prothrombin, factor XII and Macrophage Stimulating Factor (MSF).[28,29]

Lipoprotein(a) shares a high degree of sequence identity with plasminogen.[30] It competitively binds to the plasminogen receptor, thus reducing the activity of plasminogen.

The apoprotein gene is highly polymorphic, more than thirty four (34) different sized alleles have been identified.[31] Molecular weight ranges from 187-648 kilodalton (KDa).[32,33]

Plasma **lipoprotein(a)** concentration varies inversely with the size of apoprotein isoform.[34] Smaller isoforms are usually associated with higher total **lipoprotein(a)** levels and a higher risk of atherogenicity.[35]

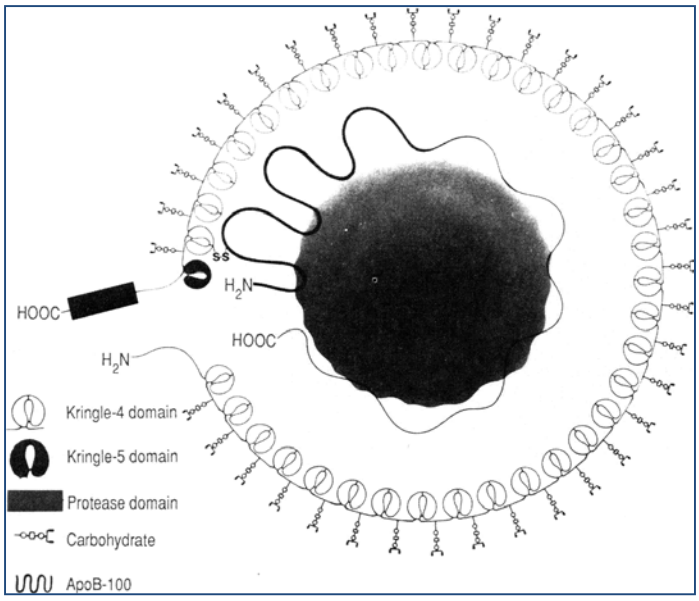
The most important factor in determining **lipoprotein(a)** levels is apoprotein(a) gene locus. It accounts for 90% of variation of plasma **lipoprotein(a)** levels.[36]

Apoprotein(a) consist of a series of tandemly repeated modules known as kringles, that are commonly found in many proteins involved in fibrinolytic and coagulation cascades such as plasminogen and thrombin respectively.[26]

Specifically, apoprotein(a) contains multiple tandem repeats of domain similar to plasminogen kringle IV followed by sequences similar to kringle V and protease domain of plasminogen.

Kringles are triple looped cysteine linked amino acid domains. They are held together by the formation of three internal disulphide bonds. Ten types of kringle IV (KIV_{1-10}) like domains are found in apoprotein(a).

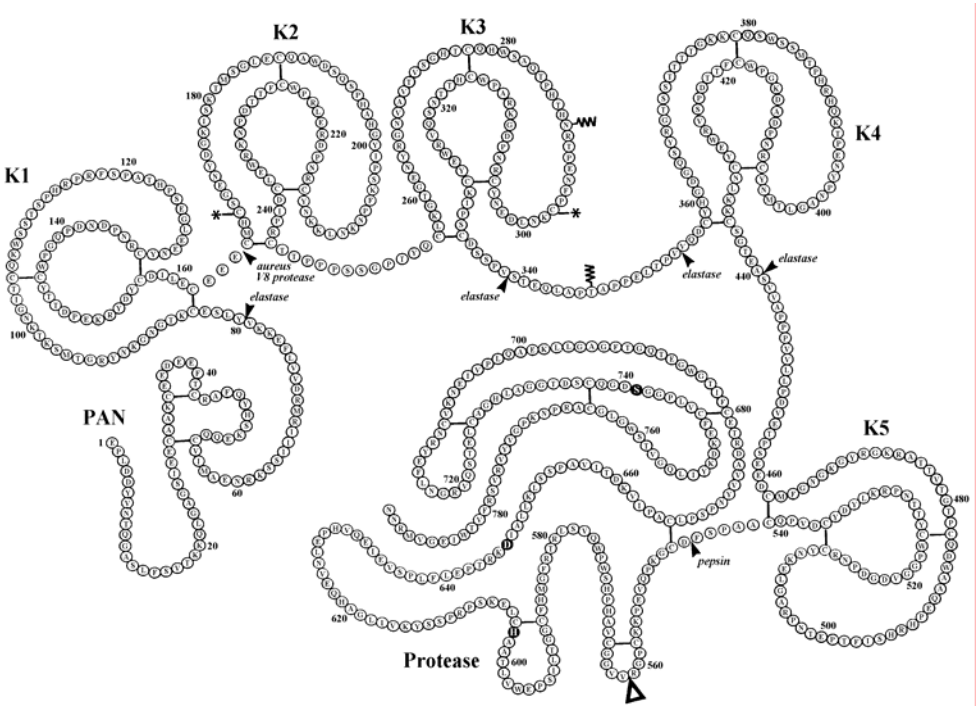
Structure of lipoprotein(a)



HUMAN PLASMINOGEN

Plasminogen is the precursor of the anticoagulant protein plasmin. A single human plasminogen peptide chain consists of 791 amino acid residues and two carbohydrates attached to the peptide chain by the presence of disulphide bonds. Plasminogen's structure is divided into a contiguous series of five homologous regions called **Kringles.** Human plasminogen consists of an amino terminal peptide, five kringle modules and a protease domain.

The apoprotein(a) gene contains a single protease domain that is 94% identical to the protease domain of the plasminogen gene. It also contains two plasminogen like kringle domains one of them homologous to kringle 4 and the other kringle 5.



DIFFERENCES BETWEEN APOPROTEIN(a) AND PLASMINOGEN

1. Unlike plasminogen, apoprotein(a) cannot be converted to an active protease by tissue plasminogen activator, streptokinase or urokinase. This is due to single amino acid substitution in apoprotein(a) that makes it resistant to the activity of these proteases.

2. Presence of one single unpaired cysteine residue of apoprotein(a) to facilitate binding to apoprotein B-100. Lipoprotein(a) is very rich in carbohydrate containing 28.1% carbohydrate by weight.

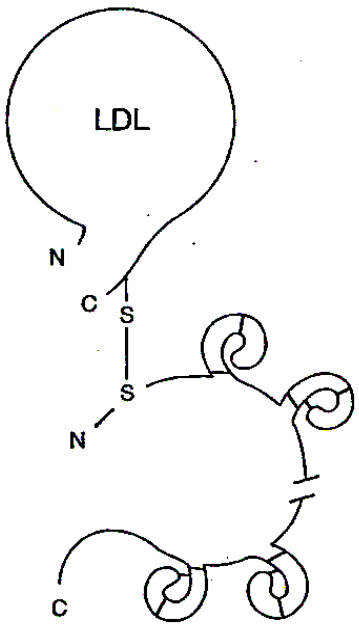


FIG. 6. The structure of lipoprotein (a). The apolipoprotein(a) moiety is located in the lower portion of the diagram together with four of its representative kringle (triple-loop) domains. Apolipoprotein(a) is linked to low density lipoprotein by a single disulfide bridge. (From Loscalzo J, Weinfeld M, Fless GM, Scanu AM. Lipoprotein(a), fibrin binding, and plasminogen activation. *Arteriosclerosis* 1990; 10:240–245, with permission.)

GENETICS, RACE AND NORMAL LEVEL

Levels of **lipoprotein(a)** are largely genetically determined, does not show significant variation with age and it varies with race and ethinicity.[37]

At birth, **lipoprotein(a)** levels are reported to be low. In newborns, it is not related to gender or race as in adults. Serum **lipoprotein(a)** concentration increases

during first year of life and reaches the adult concentration by the second year.[38] Thereafter no variation with age occurs. Levels are higher in Asians and Africans when compared to white population in Framinhgham study. Levels above 30 mg/dl are generally considered as elevated.

MODULATION OF PLASMA LIPOPROTEIN(a) CONCENTRATION

There was no significant correlation of **lipoprotein(a)** levels with age, height, Body Mass Index, total cholesterol, high density lipoprotein(HDL) or low density lipoprotein(LDL)[39].

The level of **lipoprotein(a)** is increased in diabetes mellitus, chronic renal failure, nephrotic syndrome, malignancy, menopause, and hypothyroidism. **Lipoprotein(a)** levels is decreased in liver cell failure and hyperthyroidism. Diet, weight loss and exercise have no effect on **lipoprotein(a)** levels.

Smaller or no difference at all in lipoprotein concentration were noted between males and females in different adult population. Mean levels of **lipoprotein(a)** in a normal population were 14 mg/dl for men and 15mg/dl for women as given by recent Framingham Study.

SYNTHESIS AND METABOLISM OF LIPOPROTEIN(a)

The dominant effect on the serum concentration of **lipoprotein(a)** is exerted by the rate of hepatic secretion[40]. This is consistent with the fact that after

heterologous liver transplantation, apoprotein(a) phenotype changes to that of the donor[41]. So, patients with liver disease and alcohol abuse will have low **lipoprotein(a)** levels[42].

The most important factor in determining the **lipoprotein(a)** levels is apoprotein(a) gene locus.

The assembly of **lipoprotein(a)** is extracellular.[43,44] Newly synthesised apoprotein(a) binds to hepatocyte cell surface via its kringle domains.[45] From this location, it is captured by apoprotein B and released from the cell as lipoprotein particle. The cell surface of association of apoprotein(a) is important to prevent the release of apoprotein(a) into plasma where it may participate in potentially detrimental associations with other cell surfaces.[46]

The mechanism of **lipoprotein(a)** clearance from the circulation is much less well defined. Previously, **lipoprotein(a)** was thought to be degraded through the low density lipoprotein(LDL) receptor pathway. However, two recent studies have shown that this is not the primary pathway.[47]

Synder et al., showed that the binding and degradation of **lipoprotein(a)** by the low density lipoprotein(LDL) - receptor pathway in human hepatocytes, macrophages and fibroblast was only 10 - 30%.[48] Other pathways involved in lipoprotein(a) catabolism are less clear.

Certain in vitro studies have demonstrated that non-low density lipoprotein(LDL) receptor pathways contribute towards **lipoprotein(a)** catabolism.[48,49] Lipoprotein lipase may facilitate some of its uptake. A receptor for **lipoprotein(a)** has been demonstrated in human macrophages and glycoprotein II b on platelets. [50,51] The role of such pathways in the clearance of **lipoprotein(a)** from plasma is under study.

LIPOPROTEIN (a) IN CORONARY HEART DISEASE

Many prospective studies were conducted to find out the association of **lipoprotein(a)** and coronary heart disease.[52] It was noted that raised **lipoprotein(a)** levels were associated with the presence and severity of coronary heart disease.[53]

Children of parents with premature heart disease had higher **lipoprotein(a)** levels than children of healthy parents[54].

Lipoprotein(a) levels in restenosis is under extensive study and till date, it has yielded only conflicting results.[55] Studies by Daida et al, noted a much lower restenosis rates in patients, whose **lipoprotein(a)** levels are markedly reduced by the technique of apheresis.[56]Bruegman et al [57] and Molliterno et al,[58] suggest that **lipoprotein(a)** levels play an important role in spontaneous thrombolysis.

LIPOPROTEIN(a) AND DIABETES MELLITUS

Variation of **lipoprotein(a)** levels in diabetic individuals was studied by various research teams. Conclusions appear to vary depending on the type of diabetes. A study on 415 children aged 13-14 years with type 1 DM by Salzer et al, showed

significantly higher levels of **lipoprotein(a)** in diabetic children[59] compared with normal children. Pubertal and post pubertal patients had higher levels compared with control subjects. This observation gave way to suggestions that a rise in **lipoprotein(a)** occur during puberty in type 1 DM.[60]

Majority of studies in type 2 DM failed to show an increase in levels of **lipoprotein(a)**. It is reported that patients with type 2 DM have lower, [61, 62] higher[63, 64] or similar[65-69] **lipoprotein(a)** levels compared with non-diabetic subjects. No significant relationship between **lipoprotein(a)** levels and glycemic control was noted in the group of type 2 DM .[70,71]

LIPOPROTEIN(a) AND KIDNEY

Markedly elevated **lipoprotein(a)** levels have been described in all kinds of renal disease and their treatment modalities. On an average, **lipoprotein(a)** levels are elevated six times in nephrotic syndrome[72], two to three fold in patients receiving hemodialysis or peritoneal dialysis as compared to healthy controls.[73,74]

It was suggested that elevation of **lipoprotein(a)** occur early in renal failure, or alternatively, elevated **lipoprotein(a)** levels may promote progression to chronic renal failure.[75] Renal transplantation in end stage renal failure is accompanied by a

significant decrease in **lipoprotein(a)**.[75] Irish et al found that the type of treatment of chronic renal failure influences the plasma level of **lipoprotein(a)**. The patients on continuous ambulatory peritoneal dialysis showed significant increase in **lipoprotein(a),** when compared to hemodialysis.

DRUGS AND LIPOPROTEIN (a)

Lipid lowering drugs like statins and resins does not have any effect on **lipoprotein(a)**. Estrogen replacement therapy in post menopausal women lowers **lipoprotein(a)**.[76,77] High dose (3-4 gm/day) niacin has been reported to lower **lipoprotein(a)** by 35-50%.[78] Linus Pauling suggested that Vitamin C does lower **lipoprotein(a)** levels. Fenofibrate has shown some **lipoprotein(a)** lowering effect in recent studies by 14%. There is no larger scale trial available supporting this study.[79]

LIPOPROTEIN(a) - ASSOCIATION WITH OTHER THROMBOTIC RISK FACTORS

LIPOPROTEIN(a) AND FIBRINOGEN

Serum **lipoprotein(a)** levels correlate significantly with plasma fibrinogen levels in some studies, but not in all.[80,81] Platelet activity is enhanced by fibrinogen and raised plasma fibrinogen concentrations are predictors of vascular events.[82,83]

There is a strong evidence that fibrinogen is an independent risk factor for ischemic atherothrombotic stroke.[84]It is also associated with increased risk of

recurrent vascular events.[85] Fibric acid derivatives used to reduce circulating concentrations of **lipoprotein(a)** also reduce levels of serum fibrinogen.[86]

LIPOPROTEIN(a) AND HOMOCYSTEINE

A moderate increase in circulating homocysteine concentration is associated with an increased risk of atherosclerosis and venous thrombosis.[87,88] Concomitant rise of lipoprotein(a) and homocysteine has shown to increase the risk of vascular events.[89]

Both **lipoprotein(a)** and homocysteine exhibit effects on platelets, coagulation and fibrinolysis. Homocysteine increase platelet aggregability and promote vasoconstriction through thromboxane A2 release.[90] Homocysteine is a strong predictor of ischemic stroke.[91] The levels of homocysteine is influenced by renal function and vitamin B12 status. [92]

Homocysteine, **lipoprotein(a)** and fibrinogen interact together to promote atherogenesis.[93] The clustering of all the three increases the risk of vascular events. Epidemiological studies indicate that dyslipidemia + raised **lipoprotein(a)** and dyslipidemia + raised fibrinogen combination increase the risk of vascular events.[94,95,96]

LIPOPROTEIN(a) AND STROKE

The possibility of **lipoprotein(a)** as a risk factor for ischemic stroke has been assessed in several case control and retrospective studies. The results differ and are not conclusive.

STUDIES SUPPORTING LIPOPROTEIN(a) AS A RISK FACTOR FOR STROKE

In a case control study [Jurgens G et al, **lipoprotein(a)** in ischemic cerebrovascular disease - a new approach to the assessment of risk for stroke. Neurology 1987], serum **lipoprotein(a)** levels were significantly ($p < 0.001$) higher in patients with ischemic stroke compared with healthy individuals.[97]

Lindgren et al, determined lipid variables in 131 patients six months after stroke.[98] These patients had higher triglycerides and **lipoprotein(a)** levels and lower total cholesterol, low-density lipoprotein and high-density lipoprotein concentrations compared with controls.

In a study conducted in 45 patients with stroke (younger than 55 years) and their first degree relatives by Vavernova et al, **lipoprotein(a)** levels were reported to be genetically conditioned in patients with ischemic stroke.[99]

Jurgens et al, determined **lipoprotein(a)** and apoprotein phenotypes in a consecutive series of 265 patients with ischemic stroke in comparison with 288 controls.[100]They suggested that raised **lipoprotein(a)** concentrations comprise a primary risk associated with the presence of this disease.

Van Kooten and colleagues[101] assessed **lipoprotein(a)** concentrations in 151 consecutive patients admitted because of acute cerebral ischemia. They found that in about one third of patients **lipoprotein(a)** levels were significantly raised.

Peynet et al, evaluated the **lipoprotein(a)** concentrations and apo(a) isoform size in 90 young individuals (mean age 37.4) with acute cerebral ischemia compared with age and sex matched individuals. They showed that serum lipoprotein levels were significantly ($p<0.009$) elevated in patients with stroke.[102]

Nagayama et al, in a case control study, [103] investigated **lipoprotein(a)** levels in patients after a period of 27 months since their stroke . They concluded that **lipoprotein(a)** was a crucial and independent risk factor for ischemic stroke.

In the Atherosclerosis Risk In Communities (ARIC) study, [104] the association of **lipoprotein(a)** with stroke was investigated in 15,160 participants. In this study, **lipoprotein(a)** was an independent risk factor for stroke and TIA.

STUDIES NOT SUPPORTING LIPOPROTEIN(a) AS A RISK FACTOR FOR STROKE

Hachinski et al, [105] determined lipid variables, including **lipoprotein(a)** in 80 patients with stroke or Transient Ischemic Attacks(TIA). Increased low density lipoprotein(LDL) and triglyceride(TG) concentrations correlated with atherothrombotic stroke risk, whereas no statistical significance was noted with **lipoprotein(a)**.

In a study conducted by Glades et al, [106] no association between baseline plasma **lipoprotein(a)** levels and future ischemic cerebral infarct was noted.

In a prospective study in Finland, no association was found between **lipoprotein(a)** levels and atherosclerotic disease.[107]

In a cohort study, 14,916 persons were followed prospectively for a period of 7.5 years. No association between baseline plasma concentration of **lipoprotein(a)** and future risk of thromboembolic stroke was found. [108]

LIPOPROTEIN(a) PATHOPHYSIOLOGY AS AN ATHEROTHROMBOGENIC FACTOR

ATHEROGENICITY

a. **Lipoprotein(a)** plays an important role in the initiation, progression and subsequent rupture of atherosclerotic plaque.[109]

b. The accumulation of **lipoprotein(a)** molecules has been demonstrated in the arterial walls of human coronary and cerebral vessels.[110]

c. Apoprotein(a) has a tendency to bind to connective tissue elements like proteoglycans, glycosaminoglycans and fibronectin.[111] This binding is promoted by **lipoprotein(a)** lipase or sphingomyelinase.[112]

d. **Lipoprotein(a)** particles undergo oxidative modification and scavenger receptor uptake, leading to intracellular accumulation and foam cell formation in vascular endothelium.[113,114]

e. The process of increased atherogenicity of **lipoprotein(a)** is similar to the role played by low density lipoproteins(LDL) in the formation of atherosclerotic plaque.

THROMBOGENICITY

a. The apoprotein moiety of **lipoprotein(a)** bears a structural homology to plasminogen.

b. **Lipoprotein(a)** competes with plasminogen for its receptors on endothelial cells. This reduces the activity of plasminogen significantly, resulting in diminished plasmin formation. This delays clot lysis and favours thrombosis.[115]

c. **Lipoprotein(a)** binds to immobilized fibrinogen and fibrin resulting in inhibition of plasminogen binding to these substrates. The high affinity of lipoprotein(a) to fibrin is the causes for its co-localisation in atherosclerotic plaque.[116]

d. **Lipoprotein(a)** enhances the synthesis of Plasminogen Activator Inhibitor (PAI-1) by endothelial cells.[117] This property of **lipoprotein(a)** contributes to its anti-fibrinolytic activity.

e. **Lipoprotein(a)** displaces plasminogen from the surface of macrophages in atherosclerotic plaques and it reduces the activation of latent Transforming Growth Factor β (TGF- β). In the absence of activated TGF- β, cytokines induces smooth muscle proliferation.[118]

ENDOTHELIAL DYSFUNCTION

High levels of **lipoprotein(a)** is also associated with endothelial dysfunction. This endothelial dysfunction is enhanced by lipid deposition in vessel walls, inhibiting fibrinolysis and modulating smooth muscle proliferation.[119]

ATHEROSCLEROSIS IN INTRACRANIAL ARTERIES

Intracranial arteries are relatively resistant to cholesterol related endothelial damage.[120]

a. Studies on human necropsy has shown that atherosclerotic changes in cerebral arteries make their appearance 20 years later than in coronary arteries.[121]

b. Recent study by Landray et al, in stroke patients underlined low density lipoproteins((LDL) score to have a borderline significance.[122]

c. In another experimental model by Wullian et al, high **lipoprotein(a)** levels were associated with occlusive arterial thrombosis in intracranial vessels and may also causes permanent cessation of flow.[123]

d. Analysis of damaged arterial segments indicated incorporation of **lipoprotein(a)** into adventitia, media and intima.[123]

e. Watts and colleagues et al showed raised **lipoprotein(a)** concentrations were a significant determitant of the carotid atherosclerosis.[124]

f. Endothelial dependent vasomotor tone is also related to **lipoprotein(a)** levels but its clinical implications are not yet determined (Delanty etal). [125]

MATERIALS AND METHODS

The study was conducted in Thanjavur Medical College Hospital, Thanjavur, Tamilnadu. The study was conducted in the Department Of Internal Medicine. The study period extended between June 2007 and October 2008. It was a carefully selected study population of stroke, purely ischemic in patients aged forty years or less, without any other identifiable risk factors. The patients were selected on the basis of inclusion and exclusion criteria. In all those patients, **lipoprotein(a)** was estimated and discussed later. The study included both sexes.

The control population included similar age group in both sexes and without any identifiable risk factor. The control group was selected from the inpatient population of medical wards.

A total number of 25 cases have satisfied the criteria for the study group.

INCLUSION CRITERIA

Two absolute inclusion criteria are

1) Age forty years or less

2) CT scan showing purely ischemic infarcts.

Patients of both sexes, with family history of stroke and history of recurrent stroke were also included in the study.

EXCLUSION CRITERIA

1. Age greater than 40 years
2. CT brain showing hemorrhage
3. Hypertensive (BP >140/90mm Hg)
4. Diabetics
5. Valvular heart disease
6. ECG / ECHO evidence of CAHD (Coronary Artery Heart Disease)
7. VDRL - reactive
8. HIV - reactive

9. Malignancy
10. Lipid lowering drugs
11. Rheumatoid arthritis
12. Renal failure
13. Diabetic nephropathy
14. Nephrotic syndrome
15. Liver cell disease
16. Thyroid dysfunction (hypothyroidism / hyperthyroidism).

A proforma was drafted including the details about the presenting illness and specifically related to known risk factors and factors that can elevate **lipoprotein(a)**. History of recurrent stroke, Transient Ischemic Attacks and history of stroke in family members were enlisted.

All patients were subjected to routine physical examination. Body Mass Index (BMI) was calculated for every person.

CT scan brain and repeat CT scan (if needed) was done and the reports were included. The results of VDRL and HIV were entered.

Routine blood investigations like complete hemogram, blood sugar (random and fasting), blood urea, serum creatinine, erythrocyte sedimentation rate, packed cell volume and complete urine examination were done.

The levels of **lipoprotein(a)** was entered in the proforma.

METHODOLOGY

Lipoprotein(a) Estimation

The sample was withdrawn after a period of over night fasting. 5ml of venous blood was collected in a sterile glass tube. The blood was allowed to clot, centrifuged and analysed for **lipoprotein(a)** levels using NEPHELOMETRY method.

NEPHELOMETRY

Nephelometry is defined as the detection of light energy scattered towards a detector that is not in the direct path of the transmitted light. Common nephelometers available measure scattered light at right angles to the incident light. Some of them have detectors placed at angles of 60°-70°.

This enables to take advantage of the increased forward scatter intensity caused by light scattering from large particles. The amount of light scattered is proportional to the concentration of antigen or antibody in the solution.

Nephelometry is one the most commonly used technology for protein assays such as apolipoproteins, lipoprotein(a), C-reactive protein, rheumatoid factor, anti-Streptolysin O, C_3, C_4, immunoglobulins etc., Other method commonly used is turbidimetry.

Nephelometry methods are more sensitive than turbidimetry with a detection of approximately 10µg/ml, whereas detection limit of turbidimetry is 20-30µg/ml. Nephelometry shows a slightly better detection limit in lipemic samples.

RESULTS AND ANALYSIS

The study population included 25 young ischemic stroke patients with 23 males and 2 females matched with 25 age and sex matched controls. All patients were admitted to medical wards and discharged after an average period of 5 days.

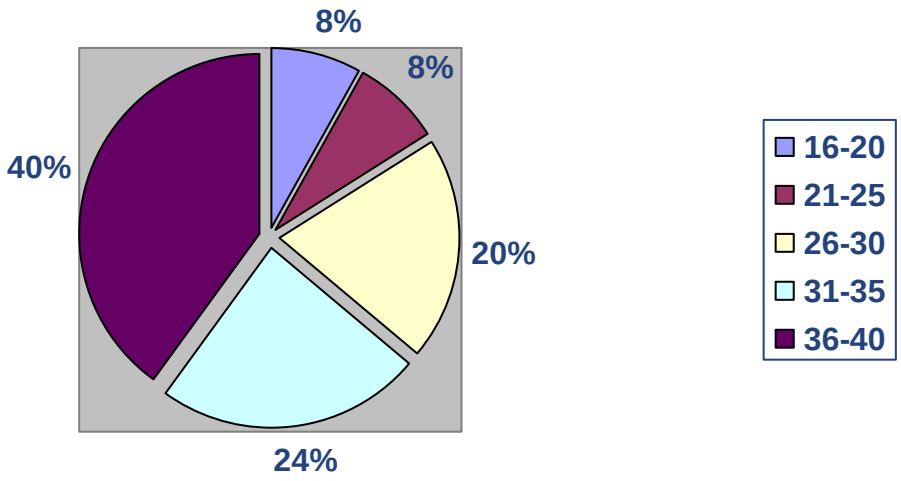
AGE INCIDENCE

Table 1

Age in years	16-20	21-25	26-30	31-35	36-40
No. of cases	2	2	5	6	10
Percentage	8%	8%	20%	24%	40%

Fig 1

AGE INCIDENCE-TOTAL POPULATION



SEX INCIDENCE

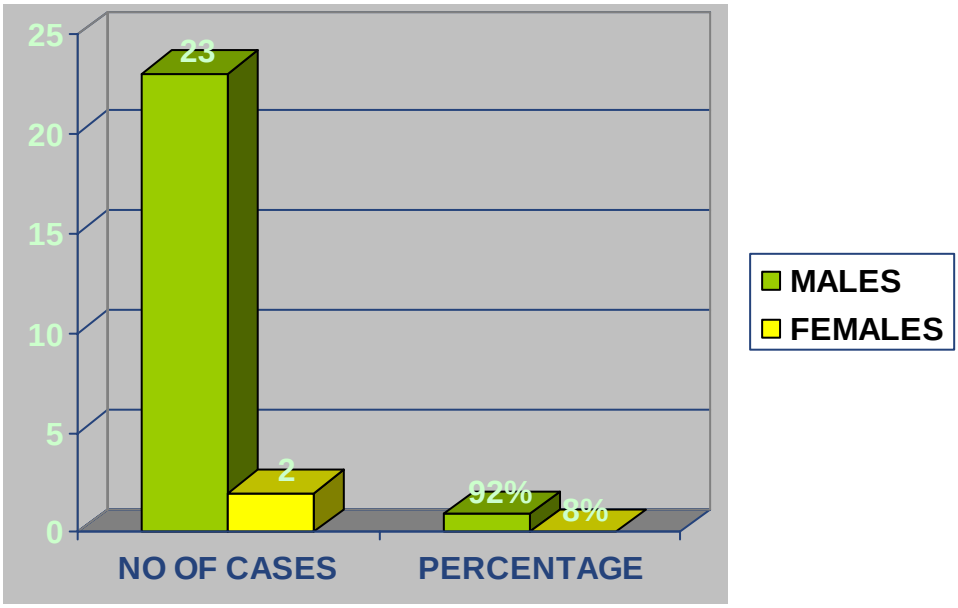
Our study group included twenty three males and two females.

Table 2

SEX	NO. OF CASES	PERCENTAGE
MALES	23	92%
FEMALES	2	8%

Fig 2

SEX INCIDENCE - TOTAL POPULATION



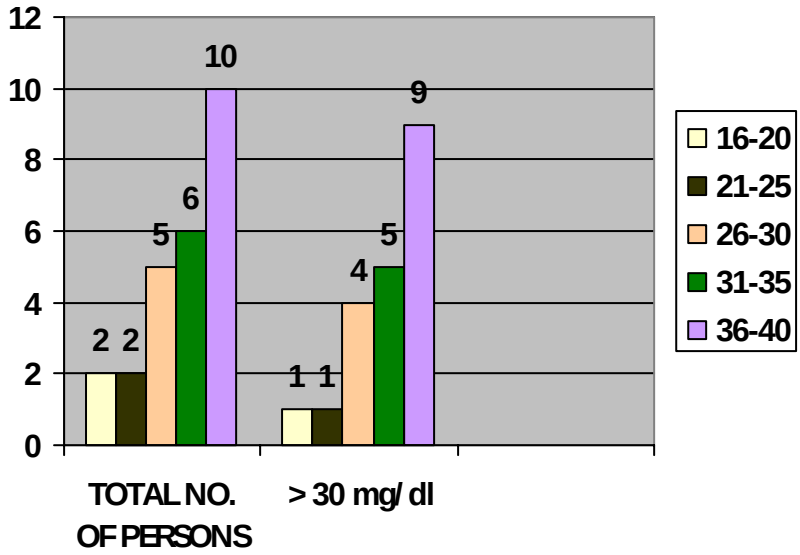
LIPOPROTEIN(a) LEVELS ACCORDING TO AGE IN STUDY GROUP

Table 3

AGE(YEARS)	NO. OF PERSONS	LIPOPROTEIN(a) >30 mg / dl.	PERCENTAGE
16-20	2	1	50%
21-25	2	1	50%
26-30	5	4	80%
31-35	6	5	83%
36-40	10	9	90%

Fig 3

STUDY GROUP



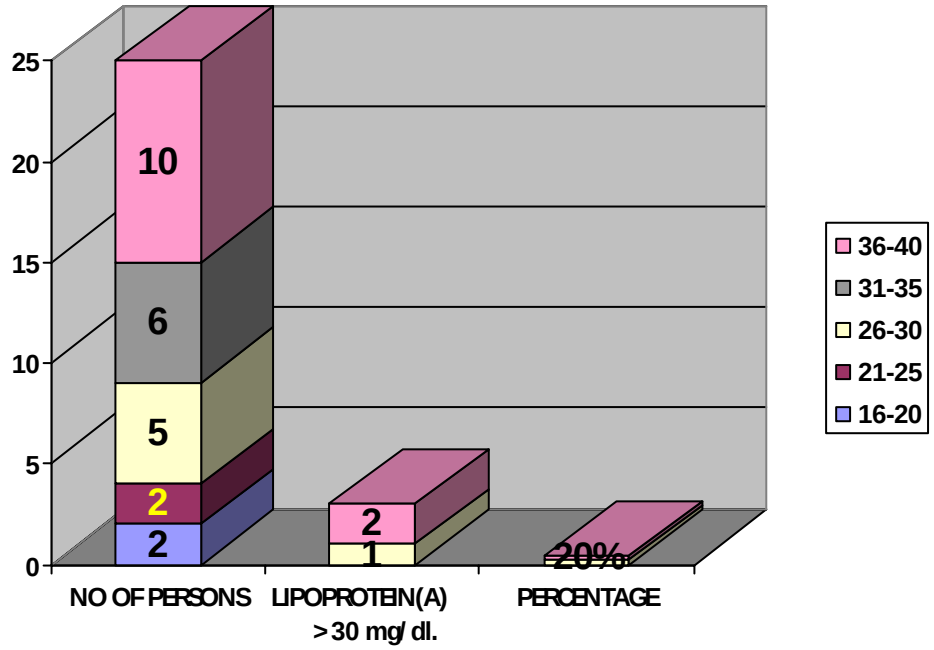
LIPOPROTEIN(a) LEVELS ACCORDING TO AGE IN CONTROL GROUP

Table 4

AGE (YEARS)	NO OF PERSONS	LIPOPROTEIN(a) > 30 mg/dl.	PERCENTAGE
16-20	2	-	-
21-25	2	-	-
26-30	5	1	20%
31-35	6	-	-
36-40	10	2	20%

Fig 4

CONTROL GROUP



LIP

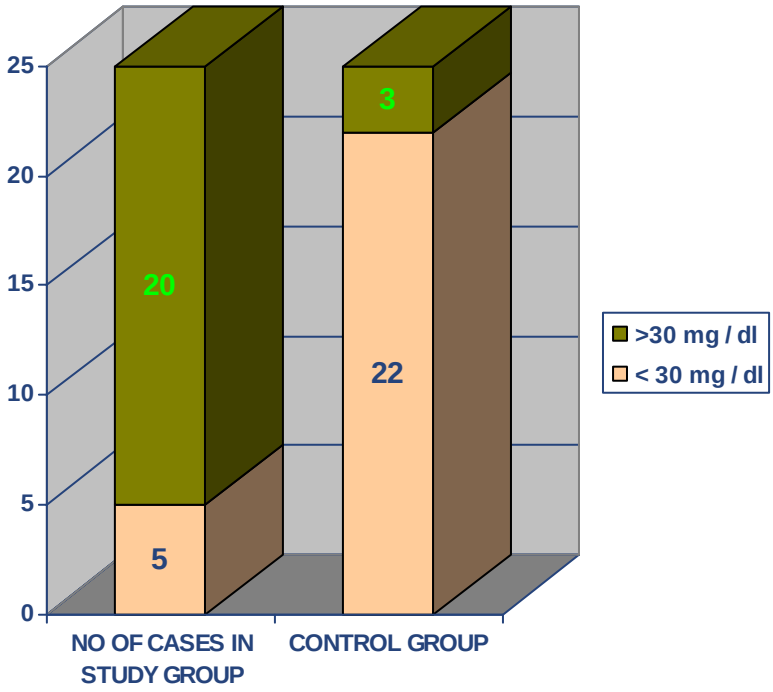
OPROTEIN(a) LEVELS IN CONTROL AND STUDY POPULATION

Table 5

LIPOPROTEIN(a)	NO OF CASES IN STUDY GROUP	CONTROL GROUP
< 30 mg / dl	5	22
>30 mg / dl	20	3

Fig 5

STUDY AND CONTROL GROUP



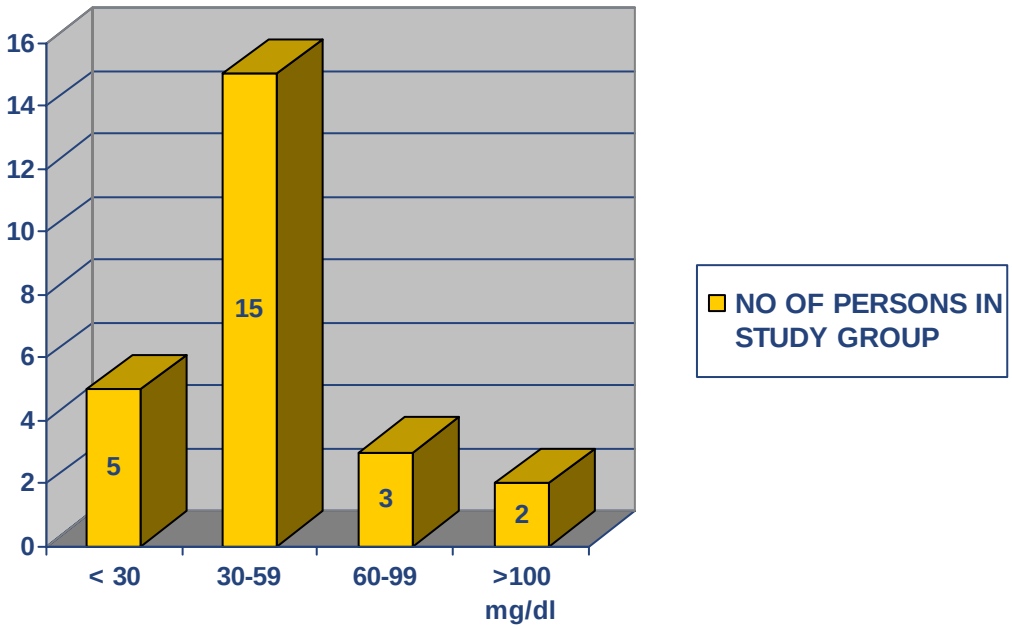
DISTRIBUTION OF PATIENTS ACCORDING TO LIPOPROTEIN(a) LEVELS IN STUDY GROUP

Table 6

LIPOPROTEIN(a) mg/dl	**< 30**	**30-59**	**60-99**	**>100**
NO OF PERSONS IN STUDY GROUP	**5**	**15**	**3**	**2**

Fig 6

STUDY GROUP



DISTRIBUTION OF PATIENTS ACCORDING TO LIPOPROTEIN(a)

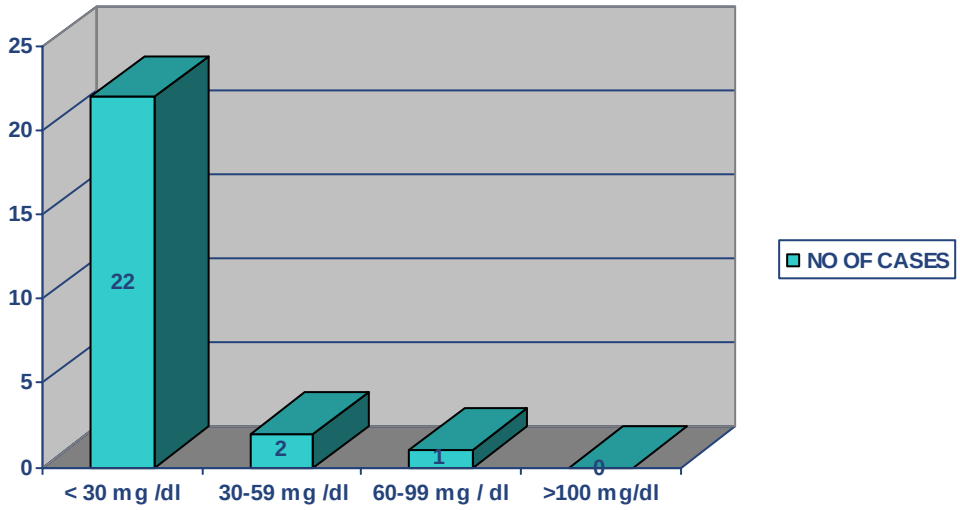
LEVELS IN CONTROL GROUP

Table 7

LIPOPROTEIN(a)	< 30 mg /dl	30-59 mg /dl	60-99 mg / dl	>100 mg /dl
NO OF CASES	22	2	1	0

Fig 7

CONTROL GROUP



DISTRIBUTION OF LIPOPROTEIN(a) IN MALES AND FEMALES

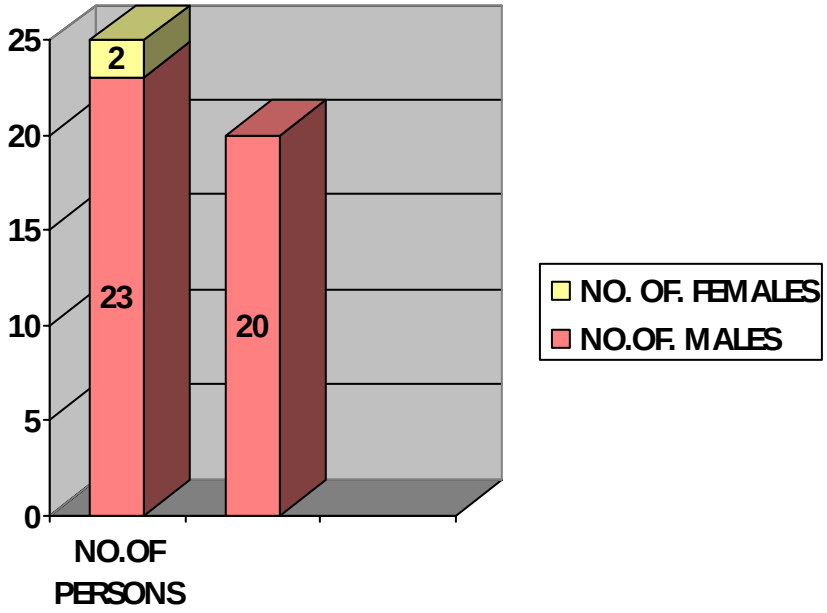
IN STUDY GROUP

Table 8

SEX	NO OF PERSONS	LIPOPROTEIN(a) >30mg/dl
NO.OF. MALES	23	20
NO. OF. FEMALES	2	0

Fig 8

STUDY GROUP



DISTRIBUTION OF LIPOPROTEIN(a) IN MALES AND FEMALES

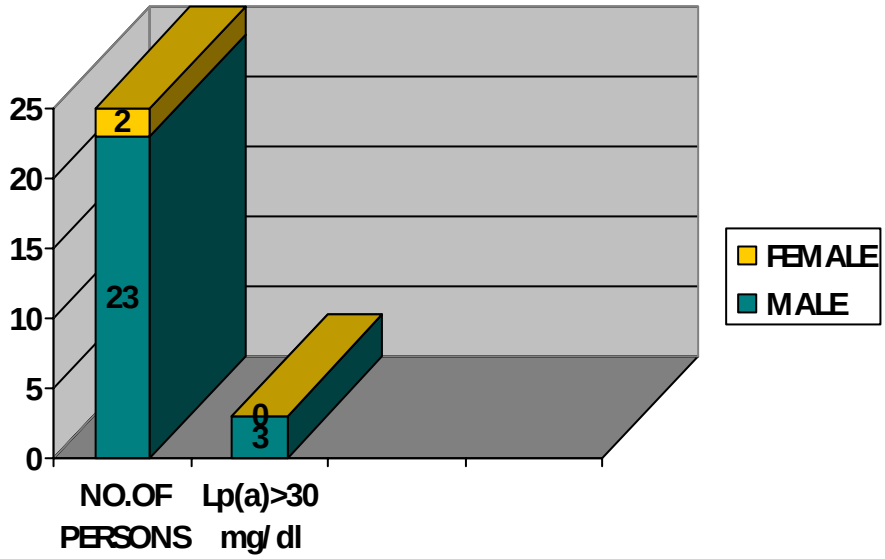
IN CONTROL GROUP

Table 9

SEX	NO. OF PERSONS	LIPOPROTEIN(a) >30 mg/dl
MALE	23	3
FEMALE	2	0

Fig 9

CONTROL GROUP

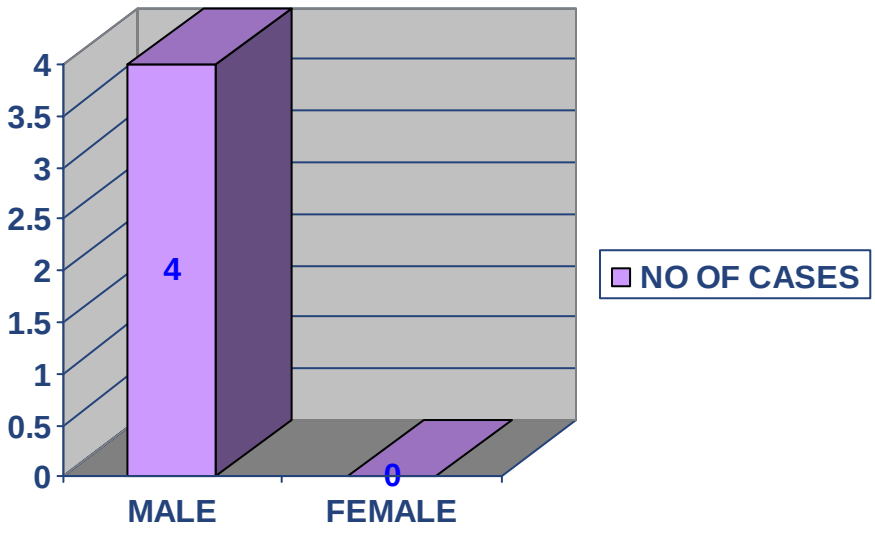


INCIDENCE OF RECURRENT STROKE IN STUDY GROUP

Table 10

RECURRENT STROKE	MALE	FEMALE
NO OF CASES	4	0

Fig 10



STATISTICAL ANALYSIS

GROUP	>30 mg/dl	< 30 mg/dl	TOTAL
STUDY GROUP	20	5	25
CONTROL GROUP	3	22	25
TOTAL	23	27	50

Using chi-square, p value was derived. It was found to be < 0.001, which is highly statistically significant.

Hence the **lipoprotein(a)** levels noted in our study population of young ischemic stroke assume statistical significance.

AGE AND LIPOPROTEIN(a)

Analysis of study group

The highest **lipoprotein(a)** level noted in our study was 109 mg/dl. It was observed in the age group of 21-25years. The patient was 23years of age.

The lowest **lipoprotein(a)** level of <10 mg/dl was noted in 5 patients equally distributed in all the five age groups.

The mean **lipoprotein(a)** level in each group is

16-20 years	**23 mg/dl**
21-25 years	**59.5 mg/dl**
26-30 years	**45.32 mg/dl**
31-35 years	**40.38 mg/dl**
36-40 years	**49.65 mg/dl**

The mean **lipoprotein(a)** was found to be the highest in the age group of 21-25 years with a level of 59.5 mg/dl. This was entirely contributed by the highest level of 109 mg/dl observed in the study. The mean **lipoprotein(a)** level was below the cut-off mark of 30 mg/dl, only in the age group of 16-20years. All the other age group showed an increase in the mean **lipoprotein(a)** level.

Analysis of Control Group

The highest level of **lipoprotein(a)** in the control group was 63mg/dl. It was noted in the age-group of 26-30 years. The patient was 27 years of age.

The lowest level of <10 mg/dl was noted in three patients.

The mean **lipoprotein(a)** of the control group in each age group is

16-20 Years	**14.2 mg /dl**

21-25 Years	**17.4 mg /dl**
26-30 Years	**30.89 mg /dl**
31-35 Years	**18.33 mg /dl**
36-40 Years	**26.18 mg /dl**

The mean **lipoprotein(a)** level of 26-30 years age group was slightly above the cut-off level of 30mg/dl. The mean **lipoprotein(a)** of other age groups fell below the cut off level of 30mg/dl.

SEX DISTRIBUTION

The study population comprised 23 males and two females, matched with the control group in a similar proportion.

Lipoprotein(a) and sex

In study group

Out of the 23 males with ischemic stroke, three did not show an increase in **lipoprotein(a)** level. The two female in the study population had levels of less than 10 mg /dl.

The mean **lipoprotein(a)** in male is 48.27 mg /dl.

The mean **lipoprotein(a)** in female is less than 10 mg /dl.

Lipoprotein(a) and sex

In control Group

Out of the twenty three males included in the control group, only three had elevated lipoprotein(a) levels. Both the female had lipoprotein(a) levels less than 30 mg/dl.

The mean **lipoprotein(a)** in male is 24.23 mg /dl. The mean **lipoprotein(a)** in female is 16 mg /dl.

AGE DISTRIBUTION

In Study Group

The study population included ischemic stroke patients aged forty years or less. The youngest of the study group aged 18 years and the eldest was 40 years of age. The mean age was 35years.

Out of the 25 stroke patients included in the study, 10 fall into the age group of 36-40 years. The age group of 16-20 years and 21-25 years comprised 8% of the study population.

This is consistent with the fact that as age increases, the risk of stroke increases and age is the single most important predictor of stroke.

In Control Group

The control group of 25 individuals were age matched and sex matched. The distribution of 25 control group population according to age group is similar to that of the study group.

16-20 years	**2**
21-25 years	**2**
26-30 years	**5**
31-35 years	**6**
36-40 years	**10**

The youngest of the control group was 16 years of age and the eldest was 40 years of age.

The mean age of the control group was 31.76 years and the median age calculated was 34 years.

DISCUSSION

Analysis of lipoprotein(a) levels in young ischemic stroke patients

In the study group of 25 young ischemic stroke patients and the 25 age and sex-matched controls, **lipoprotein(a)** levels were analysed. In the study group, the **lipoprotein(a)** level was elevated in twenty of the twenty-five stroke patients.. The **lipoprotein(a)** levels ranged from less than 10 mg/dl to 109 mg/dl. The mean **lipoprotein(a)** level was higher than the cut off level of 30 mg/dl.

Inference: Lipoprotein(a) levels were elevated in young ischemic stroke.

The above inference of our study is supported by the studies of,

1. Vavernova et al 1993, [99]

2. Peynert et al 1999,[102]

3. Nagayama et al 1994,[103] These studies have concluded that the levels of **lipoprotein(a)** is significantly raised in young ischemic stroke.

Lipoprotein(a) as an independent risk factor

This study is carried out in non-diabetic and non-hypertensive young stroke patients. Even in young patients, next to age, hypertension and diabetes – the two conventional risk factors are the most important causes for ischemic stroke.

Excluding these two risk factors in our study, gave us a chance to explore the newer risk factor-**lipoprotein(a)**. Eliminating these two risk factors also made this study result much more reliable. The elevated **lipoprotein(a)** levels in our study group was statistically significant.

Inference: Lipoprotein(a) is an independent risk factor in young ischemic stroke.

The study result is well supported by the studies of

1. Zenker et al 1986, [3]

2. Nagayama et al 1994, [103]

3. Atherosclerosis Risk In Communities (ARIC) study 1994.[104]

All the above studies conclude that **lipoprotein(a)** is an independent risk factor and a predictor of stroke.

Levels of lipoprotein(a) in study and control population

The study group of young ischemic patients was compared with age and sex matched controls. Hence the two important confounding variables, age and sex were eliminated. The mean **lipoprotein(a)** in the study group was 20.84 mg/dl more than the control group.

Eighty percentage of our study group (80%) and twelve percentage (12%) of our control group had elevated **lipoprotein(a)** levels. A *p* value of <0.001 was derived, denoting the statistical significance of such elevated **lipoprotein(a)** levels in study group.

Inference: The levels of **lipoprotein(a)** was statistically higher in study group when compared with control group

This inference of our study is supported by the results of the studies of Peyner et al, [102] and Jurgens et al.[100]

Both these studies compared **lipoprotein(a)** levels of ischemic stroke patients with that of controls. They concluded that **lipoprotein(a)** levels are elevated significantly in study group .

Lipoprotein(a) variation with age

The highest level of **lipoprotein(a)** observed in our study group was 109 mg/dl. This level was noted in a 23 year old male. The lowest level observed was less than10 mg/dl. This was noted in five persons and equally distributed in each of the five age groups.

Lipoprotein(a) levels were elevated in four of the five age groups. The mean lipoprotein level was higher in the age group of 21-25 years. This was contributed by the highest level of lipoprotein(a).The mean lipoprotein(a) level did not vary much with age groups in our study population.

The highest **lipoprotein(a)** level of control group was 63 mg /dl and the lowest was less than 10 mg /dl. The highest level was noted in the 26-30 years age. The mean **lipoprotein(a)** noted in four of the five age groups in the control population did not show any elevation .

Inference: **Lipoprotein(a)** does not vary with age.

The studies of Jenner et al, [37] report that age and sex does not have any effect on **lipoprotein(a)** levels. Our study result is supported by the above reference.

To correlate lipoprotein(a) levels in men and women

Our study population comprised of twenty three males and two females. The two females in the study group did not show any increase in **lipoprotein(a)** level. Only two of the 23 males in the study group did not have increased **lipoprotein(a)** level. In our study, the mean **lipoprotein(a)** levels in males was higher than in females. In the control group also, the mean **lipoprotein(a)** levels of males was higher than that of females. However, the females comprised only 8 % of study population. The sample size was too small to note that this difference is significant.

Inference: **Lipoprotein(a)** levels in males is higher than in females. The reliability of this association is weak and statistical significance could not be noted.

Relationship of lipoprotein(a) levels to recurrent ischemic stroke

Four of our stroke patients had history of stroke previously. All of them had ischemic infarcts. All the four patients had elevated **lipoprotein(a)** levels. Two of them had levels greater than 100 mg/dl. Both were non smokers. And in both of them no other risk factors were present. Thus, elevated lipoprotein levels could be taken as a predictor of recurrent stroke. Studies associating **lipoprotein(a)** levels to recurrent ischemic stroke are lacking. This offers us scope for further studies to assess whether elevated **lipoprotein(a)** is a predictor of recurrent strtoke.

CONCLUSION

1. The levels of **lipoprotein(a)** are elevated in young ischemic stroke.

2. **Lipoprotein(a)** is an independent risk factor for young ischemic stroke.

3. **Lipoprotein(a)** levels are higher in young ischemic stroke patients than in controls. This is statistically significant.

4. **Lipoprotein(a)** does not vary with age.

5. Men have higher levels of **lipoprotein(a)** compared to women. Larger sample of women is needed to assign statistical significance to this result.

6. **Lipoprotein(a)** levels could well be a predictor of recurrent stroke. Further studies are needed.

7. Our study results correlate well with studies, that support **lipoprotein(a)** as a possible risk factor in young stroke**.**

1. American Heart Association Heart and Stroke facts: 1994 stastical supplement. Dallas; *American Heart Association 1993.*

2. Dahlen G. Lp(a) lipoprotein in cardiovascular disease. *Atherosclerosis* 1994; 108:111-126

3. Zenker G,Koltringer P, Bone G,Niederkorn K, Pfeiffer K, Jurgens G.Lipoprotein(a) as a strong indicator for cerebrovascular disease. *Stroke* 1986; 17:942-945

4. Schreiner PJ, Chambless LE, Brown SA, Watson RL, Toole J.et al. lipoprotein (a) as a correlate of stroke and transient ischemic attack prevalence in a bi racial cohort: ARIC study.*ann Epidemiology.*1994;4:351-359

5. Nagayama m, Shinohara et al. Lipoprotein(a) and ischemic cerebrovascular disease in young adults.*Stroke.*1994; 25; 74-78.

6. Jurgens G, Taddei Peters WC, et al. Lipoprotein(a) serum concentration and apolipoprotein (a) phenotype correlate with severity and presence of stroke. *Stroke.* 1995; 26:1841-1848

7. Kario K, Matsuo T, Kobayashi H et al. silent cerebral infarction is associated with hypercoagulability, endothelial cell damage and Lp(a) levels in elderly Japanese. *Arteriosclerosis* Thrombotic Vascular Biology.1996; 16: 734-741

8. Boston AG, Gagnon DR, et al. A prospective investigation of elevated lipoprotein(a) detected by electrophoresis and cardiovascular disease in women. The Framingham Heart Study. *Circulation*.1994; 90: 1688-1695

9. Alfthan G,Pekkanen J, et al. Relation of serum homocysteine and lipoprotein(a) concentration to atherosclerotic disease in a prospective Finnish population based study.*Atherosclerosis*.1994;106:9-19.

10. Ridker PM, Stampfer MJ, et al.Plasma concentration of lipoprotein(a) and the risk of future stroke. *JAMA* 1995; 273:1269 -1273

11. Dahlen GH, Guyton JR, Attar M, Farmer JA, Kautz JA, Gotto AM. Association of levels of **lipoprotein** Lp(a), plasma lipids, and other lipoproteins with coronary artery disease documented by angiography. *Circulation* **74:** 758-765, 1986

12. Nguyen TT, Ellefson RD, Hodge DO, Bailey KR et al. Predictive value of electrophoretically detected lipoprotein(a) for Coronary artery disease and cerebrovascular disease in a community based cohort of 9936 men and women. *Circulation* 1997; 96: 1390-1397

13. Price JF, Lee AJ et al. Lipoprotein(a) and development of intermittent claudication and major cardiovascular events in men and women. *Atherosclerosis* 2001; 157: 241-249

14. Bonita R, Mendis S, Truelsen T, *et al.* The global stroke initiative. *Lancet Neurol* 2004; **3:391**–3.

15. **Truelsen T**, Bonita R, Jamrozik K. Surveillance of stroke: a global perspective. *Int J Epidemiol* 2001; **30**: S11–16

16. Department of Health and Human Services, National Centre for Health Statistics

17. Nayak SD, Nair M, Radhakrishnan K, *et al.* Ischaemic stroke in the young adult: clinical features, risk factors and outcome. *Natl Med J India* 1997; 10:107–112

18.Lee T-S, Hsu W-C, Chen C-J, *et al.* Etiologic study of young ischemic stroke in Taiwan. *Stroke* 2002; **33:1950**-1955

19.Garbusinski JM, van der Sande MAB, Bartholome EJ, *et al.* Stroke presentation and outcome in developing countries. A prospective study in the Gambia. *Stroke* 2005; 36:1388–93

20. Adams HP Jr, Kappelle LJ, Biller J, *et al.* Ischemic stroke in young adults. Experience in 329 patients enrolled in the Iowa Registry of stroke in young adults. *Arch Neurol* 1995; 52:491–5.

21. Kristensen B, Malm J, Carlberg B, *et al.* Epidemiology and etiology of ischemic stroke in young adults aged 18 to 44 years in Northern Sweden. *Stroke* 1997; 28:1702–9

22.Leys D, Bandu L, Henon H, *et al.* Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002; 59:26–33.

23.Tapas Kumar Banerjee,Shyamal Kumar DAS. Epidemiology of Stroke in India Neurology Asia 2006; 11:1-4

24. PM Dalal, Madhumita Bhattarjee- Stroke epidemic in India. Hypertension- stroke control programme is urgently needed JAPI; October 2007 vol: 55

25. Berg K. A new serum type system in man - the Lp system. *Acta Pathol Microbiol Scand* **59**: 369-82, 1963.

26. McLean JW, Tomlinson JE, Kuang WJ, et al. cDNA sequence of human apolipoprotein(a) is homologous to plasminogen. *Nature* **330:** 132-137, 1987

27.Cheng SW, Ting AC, Wong J. Lipoprotein (a) and its relationship to risk factors and severity of atherosclerotic peripheral vascular disease. Eur J Vasc Endovasc Surg 1997 ; 14: 17-23

28.Huby T, Chapman J, et al. Pathophysiological implications of the structural domain of lipoprotein(a) Atherosclerosis 1997 ;133: 1-6

29. Perombelon YFN, Soutar AK, Knight BL. Variation in **lipoprotein** (a) concentration associated with different apolipoprotein(a) alleles. *J Clin Invest* **93:**1481-92, 1994

30. Ikeo K,Takayashi K et al, Diffferent evolutionary histories of kringle and protease domains.J Mol Evol 1995; 40 331-336

31. Byrne C, Lawn R. studies on the structure and functions of apolipoprotein(a) gene. Clin gen 1994:46:34-41.

32. Van Der Hoek YY, Beisiegel et al. The apolipoprotein (a) kringle IV repeats which differ fro the major repeat kringle are present in variable isoforms. Hum Mol Genet.1993; 2:361-6

33. Albers JJ, Marcovina SM, Lodge MS. The unique **lipoprotein**(a): Properties and immunochemical measurement. *Clin Chem* **36**, 1990.

34. Albers JJ, Marcovina SM, Lodge MS. Lipoprotein(a) concentration and apolipoprotein(a) phenotypes in Caucasians and african Americans. Arteriosclero Thromb 1993; 13:1037-45

35. Seed M, Hoppichler F, Reavley D, et al. Relation of serum **lipoprotein**(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N Engl J Med* **322:** 1494- 99, 1990.

36. Gaw A, Hobbs HH. Molecular genetics of **lipoprotein**(a): new pieces to the puzzle. *Curr Opin Lipidol* **5:**149-55, 1994.

37. Jenner JL, Ordovas JM ,et al. Effects of age, sex and menopausal state on plasma lipoprotein levels.*Circulaton* 1993;87:1135-41

38. Rifai N,Heiss G, Doetsch K. Lipoprotein(a) at birth, in blacks and whites. *Arteriosclerosis* 92; 123-9, 1992.

39. Guyton JR, Dahlen GH, Patsch W, Kautz JA, Gotto JA.Relationship of plasma **lipoprotein** Lp(a) levels to race and apolipoprotein (B). *Arteriosclerosis* **5:** 265-72, 1985.

40. Krempler F, Kostner GM, Bolzano K. Turnover of **lipoprotein**(a) in man. *J Clin Invest* **65:** 1483-90, 1980.

41. Kraft H, Menzel H, Hoppichler F, Vogel W, Utermann G.Changes of genetic apolipoprotein phenotype caused by liver transplantations. Implications for apolipoprotein synthesis. *J Clin Invest* **83:** 137-142, 1989

42. Marth E, Cazzolato G, Bittolo-bon G, Avogaro P,Kostner G. Serum concentration of Lp(a) and other

lipoprotein parameters in heavy alcohol consumers. *Ann Nutr Metab* **26:** 56-62, 1982.

43. Koschinsky ML, Cote GP, Gabel B, van der Hoek YY. Identification of the cysteine residue in apolipoprotein(a) that mediates extracellular coupling with apolipoproteinB-100. *J Biol Chem* **268:** 19819-25, 1993

44. Chiesa G, Hobbs HH, Koschinsky ML, Lawn RM, Maika SD, Hammer RE. Reconstitution of **lipoprotein**(a) by infusion of human low density **lipoprotein** into transgenic mice expressing human apolipoprotein(a). *J Biol Chem* **34:** 24369-74, 1992

45. White AL, Lanford RE. Cell surface assembly of **lipoprotein** (a) in primary cultures of baboon hepatocytes. *J Biol Chem* **269:** 28716-23, 1994

46. Lawn RM, Wade DP, Hammer RE, Chiesa G, Verstuyft JG, Rubin EM. Atherogenesis in transgenic miceexpressing human apolipoprotein(a). *Nature* **360:** 670-72, 1992

47. . Liu AC, Lawn RM. **Lipoprotein** (a) and atherosclerogenesis. *Trends Cardiovasc Med* **4:** 40-44, 1994.

48. Synder ML, Hay RV, Whitington PF, Scanu AM, Fless GM. Binding and degradation of **lipoprotein** (a) and LDL by primary cultures of human hepatocytes: comparison with cultured human monocyte-macrophages and fibroblasts. *Arterioscler Thromb* **14:** 770-79, 1994.

49. Kostner GM, Grillhofer H. The interaction of Lp(a) with normal and LDL-receptor-deficient human skin fibroblasts. *Chem Phys Lipids* **67/68:**153-59, 1994.

50. Keesler GA, Li Y, Skiba PJ, Fless GM, Tabas I.Macrophage foam cell **lipoprotein**(a) / apoprotein(a)
receptor: cell-surface localization, dependence of induction on new protein synthesis, and ligand
specificity. *Arterioscler Thromb* **14:** 1337-45, 1994.

51. Malle E, Ibovnik A, Steinmetz A, Kostner GM, Sattler W. Identification of glycoprotein IIb as the **lipoprotein**(a)- binding protein on platelets: **lipoprotein** (a) binding is independent of an arginiyl-glycyl-aspartate tripeptide located in apolipoprotein (a). *Arterioscler Thromb* **14:** 345-52, 1994.

52. Cremer P, Nagel D, Labrot B, et al. **Lipoprotein** Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factor: results from the prospective Gottingen Risk Incidence and Prevalance Study (GRIPS). *Eur J Clin Invest* **24:** 444-53,1994.

53. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of **lipoprotein**(a) and the risk of myocardial infaction. *JAMA***270:** 2195-99, 1993.

54. Islam S, Gutin B, Smith C, Treiber F, MKamboh MI. Association of apolipoprotein (a) phenotypes in children with family history of premature coronary disease. *Arterioscler Thromb* **14:** 1609-16, 1994.

55. Grainger DJ, Kirschenlohr HL, Metcalfe JC, Weissberg PL, Wade DP, Lawn RM. Proliferation of human smooth muscle cells promoted by **lipoprotein** (a). *Science* **260:** 1655-68, 1993.

56. Daida H, Lee Y, Yoko‹ H, et al. Prevention of restenosis after percutaneous transluminal coronary angioplasty by reducing **lipoprotein** (a) levels with low-density **lipoprotein** apheresis. *Am J Cardiol* **73:** 1037-40, 1994.

57. Brugemann J, van der Meer J, Hillege HL, et al. **Lipoprotein** (a) levels in patients with myocardial
infarction treated with anistreplase: no prediction ofefficacy but inverse correlation with plasminogen
activation in non-patency. *Int J Cardiol* **45:** 109-13,1994.

58. Moliterno DJ, Lange RA, Meidell RS, et al. Relation of plasma liporotein(a) to infarct artery patency in survivors of myocardial infarction. *Circulation* **88:** 935-40, 1993.

59. Salzer B, Stavljenic A, Jurgens G, Dumic M, Radica A. Polymorphism of apolipoprotein E, lipporotein (a) and other lipoproteins in children with type I diabetes. *Clin Chem* **39:**1427-32, 1993.

60. Couper JJ, Bates DJ, Cocciolone R, et al. Association of **lipoprotein** (a) with puberty in NIDDM. *Diabetes Care* **16:** 689-73, 1993.

61. Haffner SM, Morales PA, Stern MP, Gruber K. Lp(a) concentrations in NIDDM. *Diabetes* **41:**1267-1272, 1992.

62. Rainwater D, W. MJ, Stern M, VandeBerg JL, Haffner S. Effects of NIDDM on **lipoprotein**(a) concentration and apolipoprotein(a) size. *Diabetes* **43:** 942-46, 1994.

63. Jenkins AJ, Steele JS, Junus ED, Santamaria JD, Best JD.Plasma apolipoprotein(a) is increased in type II
(noninsulin-dependent) diabetic patients with micro-albuminuria. *Diabetologia* **35:** 1055-59, 1992.

64. O'Brien T, Nguyen T, Harrison J, Bailey K, Dyck P,Kottke B. Lipids and Lp(a) **lipoprotein** levels and
coronary artery disease in subjects with non-insulin dependent diabetes mellitus. *Mayo Clin Proc* **69:** 430-35, 1994.

65. Csazar A, Dieplinger H, Sandholzer C, et al. Plasma **lipoprotein**(a) concentration and phenotypes in diabetes mellitus. *Diabetologia* **36:** 47-51, 1993.

66. Joven J, Vilella E. Serum levels of **lipoprotein**(a) in patients with well controlled non-insulin diabetes mellitus (Letter). *JAMA***265:** 1113-1114, 1991.

67. Velho G, Erlich D, Tuppin E, et al. **Lipoprotein**(a) in diabetic patients and normoglycemic relatives in familial NIDDM. *Diabetes Care* **16:** 742-47, 1993.

68. Bolu E, Kurt ‹, Çorakç› A, et al. ‹nsuline ba¤›ml› olmayan normoalbuminürik diabetes mellituslu olgularda serum Lp(a) düzeyleri: Metabolik kontrolle iliflkisi.
Ulusal Endokrinoloji Dergisi **6:**103-14, 1996.

69. Özer EM, Ak›n V, Kutlu H. Tip II diabetes mellitus'ta **lipoprotein**(a) düzeylerinin metabolik kontrolla iliflkisi. *Ulusal Endokrinoloji Dergisi* **5:** 21-26, 1995.

70. Çömlekçi A. Tip II diyabetik hastalarda ve sa¤l›kl› birinci derece yak›nlar›nda **lipoprotein**(a) düzeyleri ve tip II diyabetik hastalarda **lipoprotein**(a) düzeylerinin koroner anjiografi bulgular›yla iliflkisinin araflt›r›lmas› [Uzmanl›k tezi]. Dokuz Eylül Üniversitesi, 1995.

71. Çömlekçi A, Bibero¤lu S, Kozan Ö, et al. Tip II diabetes mellitus ve **lipoprotein** (a). *Türk Diabet Y›ll›¤›***12:** 129-37, 1997

72. Wanner C, Rader D, Bartens W, et al. Elevated plasma **lipoprotein**(a) in patients with the nephrotic syndrome. *Ann Intern Med***119:** 263-69, 1993.

73. Webb AT, Reaveley DA, O'Donnell M, O'Connor B, Seed M, Brown EA. **Lipoprotein**(a) in patients on
maintenance haemodialysis and continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* **8:** 609-13, 1993.

74. Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF. **Lipoprotein**(a) is an independent
risk factor for cardiovascular disease in haemodialysis patients. *Circulation* **86:** 475-82, 1992.

75. Haffner SM, Gruber KK, Aldrete GJ, Morales PA, Stern MP, Tuttle KR. Increased **lipoprotein**(a) concentrations in chronic renal failure. *J Am Soc Nephrol* **3:** 1156-1162, 1992

76. . Kim CJ, Ryu WS, Kwak JW, Park CT, Ryoo UH.Changes in Lp(a) **lipoprotein** and lipid levels after cessation of female sex hormone production and estrogen replacement therapy. *Arch Intern Med* **156:** 500-504,1996.

77. . Kim CJ, Min YK, Ryu WS, Kwak JW, Ryoo UH. Effect of hormone replacement therapy on **lipoprotein**(a) and lipid levels in postmenopausal women. *Arch Intern Med* **156:** 1693-1700, 1996.

78. Gurakar A, Hoeg JM, Kostner G, et al. Levels of lipoprotein Lp(a) decline with neomycin and niacin treatment. *Atherosclerosis.* 1985; 57:293- 301.

79.Brewer H. Effectiveness of diets and drugs in the treatment of patients with elevated lipoprotein(a) level. Scanu A : lipoprotein(a) Orlando F1 : academic Press, 1990:211.

80. Slunga L, Asplund K, Johnson O, *et al*. Lipoprotein (a) in randomly selected 25–64 year old population: the northern Sweden MONICA study. *J Clin Epidemiol* 1993;**46**:617–24.

81.Heinrich J, Sandkamp M, Kokott R, *et al*. Relationship of lipoprotein (a) to variables of coagulation and fibrinolysis in a healthy population. *Clin Chem* 1991;**37**:1950–4.

82.Mikhailidis DP, Spyropoulos KA, Ganotakis ES, *et al*. Fibrinogen and lipoprotein (a): associations in a population attending a cardiovascular risk clinic and effect of treatment with ciprofibrate. *Fibrinolysis* 1996;**10**(suppl):17.

83.Meade TW, Vickers MV, Thompson SG, *et al*. Epidemiological characteristics of platelet aggregability. *BMJ* 1985;**290**:428–32.

84.Fukujim MM, Martinez TL, Pinto LE, *et al*. Fibrinogen as independent risk factor for ischemic stroke. *Arq Neuropsiquiatr* 1997;**55**:737–40.

85.Beamer NB, Coull BM, Clark WM, *et al*. Persistent inflammatory response in stroke survivors. *Neurology* 1998;**50**:1722–8.

86.Spinler SA, Cziraky M. Lipoprotein (a): physiologic function, association with atherosclerosis, and effects of lipid-lowering therapy. *Ann Pharmacother* 1994;**28**:343–51.

87. Genest J, Jr, Malinow MR. Homocyst(e)ine and coronary artery disease. *Curr Opin Lipidol* 1992;**3**:295-9.

88.Clarke R, Daly L, Robinson K, *et al*. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med* 1991;**324**:1149–55.

89.Hopkins PN, Wu LL, Hunt SC, *et al*. Lipoprotein(a) interactions with lipid and nonlipid risk factors in early familial coronary artery disease. *Arterioscler Thromb Vasc Biol* 1997;**17**:2783–92.

90.Durand P, Lussier-Cacan S, Blache D. Acute methionine load-induced hyperhomocysteinemia enhances platelet aggregation, thromboxane biosynthesis, and macrophage-derived tissue factor activity in rats. *FASEB J* 1997;**11**:1157–68.

91.Sacco RL, Roberts JK, Jacobs BS. Homocysteine as a risk factor for ischemic stroke: an epidemiological story in evolution. *Neuroepidemiology* 1998;**17**:167–73.

92.Vila N, Deulofeu R, Chamorro A, *et al*. Plasma homocysteine levels in patients with ischemic cerebral infarction. *Med Clin (Barc)* 1998;**110**:605–8.

93.Harpel PC, Chang VT, Borth W. Homocysteine and other sulfydryl compounds enhance the binding of lipoprotein (a) to fibrin: a potential link between thrombosis, atherogenesis, and sulfydryl compound metabolism. *Proc Natl Acad Sci U S A* 1992;**89**:10193–7.

94.Cremer P, Nagel D, Labrot B, *et al*. Lipoprotein(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL cholesterol and other risk factors: results from the prospective Goettingen risk incidence and prevalence study (GRIPS). *Eur J Clin Invest* 1994;**24**:444–53.

95.Bartens W, Rader DJ, Talley G, *et al*. Lipoprotein (a) in patients with hyperlipidaemia. *Eur J Clin Invest* 1995;**25**:647–53.

96.Wild SH, Fortmann SP, Marcovina SM. A prospective case-control study of lipoprotein(a) levels and apo(a) size and risk of coronary heart disease in Stanford five-city project participants. *Arterioscler Thromb Vasc Biol* 1997;**17**:239–45.

97.Jurgens G, Koltringer P. Lipoprotein (a) in ischemic cerebrovascular disease: a new approach to the assessment of risk for stroke. *Neurology* 1987;**37**:513–15.

98.Lindgren A, Nilsson-Ehle P, Norrving B, *et al*. Plasma lipids and lipoproteins in subtypes of stroke. *Acta Neurol Scand* 1992;**86**:572–8.

99.Vavernova H, Novotny D, Ficker L, *et al*. Lipoprotein (a): a genetic risk factor for early ischemic cerebrovascular stroke. *Vnitr Lek* 1993;**39**:979–87.

100.Jurgens G, Taddei-Peters WC, Koltringer P, *et al*. Lipoprotein (a) serum concentration and apolipoprotein (a) phenotype correlate with severity and presence of ischemic cerebrovascular disease. *Stroke* 1995;**26**:1841–8.

101.Van Kooten F, van Krimpen J, Dippel DW, *et al*. Lipoprotein (a) in patients with acute cerebral ischemia. *Stroke* 1996;**27**:1231–5.

102. Peynet J, Beaudeux JL, Woimant F, *et al*. Apolipoprotein (a) size polymorphism in young adults with ischemic stroke. *Atherosclerosis* 1999;**142**:233–9

103.Nagayama M, Shinohara Y, Nagayama T. Lipoprotein (a) and ischemic cerebrovascular disease in young adults. *Stroke* 1994;**25**:74–8

104.Schreiner PJ, Chambless LE, Brown SA, *et al*. Lipoprotein (a) as a correlate of stroke and transient ischemic attack prevalence in a biracial cohort: the ARIC study. Atherosclerosis risk in communities. *Ann Epidemiol* 1994;**4**:351–9.

105.Hachinski V, Graffagnino C, Beaudry M, *et al*. Lipids and stroke: a paradox resolved. *Arch Neurol* 1996;**53**:303–8.

106.Glader CA, Stegmayr B, Boman J, *et al*. Chlamydia pneumoniae antibodies and high lipoprotein(a) levels do not predict ischemic cerebral infarctions: results from a nested case-control study in northern Sweden. *Stroke* 1999;**30**:2013–18.

107.Alfthan G, Pekkanen J, Jauhianen M, *et al*. Relation of serum homocysteine and lipoprotein (a) concentrations to atherosclerotic disease in a prospective Finnish population based study. *Atherosclerosis* 1994;**106**:9–19.

108.Ridker PM, Stampfer MJ, Hennekens CH. Plasma concentration of lipoprotein (a) and the risk of future stroke. *JAMA* 1995;**273**:1269–73.

109.Loscalzo J.Lipoprotein(a) : a unique risk factor for atherothrombotic disease. Arteriosclerosis 1990;10:672-679

110. Rath M, Niedorf A, Rablin T, *et al*. Detection and quantification of lipoprotein(a) in the arterial wall of 107 coronary bypass patients. *Arteriosclerosis* 1989;**9**:579–92.

111. Kostner GM, Bihara Varga M. Is atherogenicity of Lp(a) caused by its reactivity with proteoglycans? *Eur Heart J* 1990;**11**(suppl E):184–9.

112. Tabas I, Li Y, Brocia RW, Xu SW, *et al*. Lipoprotein lipase and sphingomyelinase synergistically enhance the association of atherogeneic lipoproteins with smooth muscle cell and extracellular matrix. A possible mechanism for low density lipoprotein and lipoprotein (a) retention and macrophage foam cell formation. *J Biol Chem* 1993; **268:20419**–32.

113.De Rijke YB, Jurgens G, Hessels EM, *et al*. In-vivo fate and scavenger receptor recognition of oxidised lipoprotein (a) isoforms in rats. *J Lipid Res* 1992;**33**:1315–25.

114.Chapman MJ, Huby T, Nigon F, *et al*. Lipoprotein (a): implication in atherothrombosis. *Atherosclerosis* 1994;**110**(suppl):S69–75.

115.Aznar J, Estelles A, Breto M, *et al*. Euglobulin clot lysis induced by tissue type plasminogen activator in subjects with increased levels and different isoforms of lipoprotein(a). *Thromb Res* 1993;**72**:459–65.

116.Smith EB, Cochran S. Factors influencing the accumulation in fibrous plaques of lipid derived from LDL. II. Preferential immobilisation of Lp(a). *Atherosclerosis* 1990;**84**:173–81.

117.Edelberg J, Reilly C, Pizzo S. The inhibition of tissue type plasminogen activator by plasminogen activator inhibitor-1. The effects of fibrinogen, heparin, vitronectin and lipoprotein(a). *J Biol Chem* 1991;**4**:2459–65.

118.Graigner DJ, Kirschenlhor HL, Metcalf JC, *et al*. Proliferation of human smooth muscle cells promoted by lipoprotein (a). *Science* 1993;**260**:1555–8.

119. Scanu AM. Atherothrombogenicity of lipoprotein (a): the debate. *Am J Cardiol* 1998;**82**:26Q–33Q.

120.Wissler RW, Vesslinovitch D. Atherosclerosis in nonhuman primates. *Adv Vet Sci Comp Med* 1977;**21**:351–420.

121. Postiglione A, Napoli C. Hyperlipidemia and atherosclerotic cerebrovascular disease. *Curr Opin Lipidol* 1995;**6**:236–42

122. Landray MJ, Sagar G, Muskin J, *et al*. Association of atherogenic low-density lipoprotein subfractions with carotid atherosclerosis. *Q J Med* 1998;**91**:345–51

123. Williams JK, Bellinger DA, Nichols TC, *et al*. Occlusive arterial thrombosis in cynomolgus monkeys with varying plasma concentrations of lipoprotein (a). *Arterioscler Thromb* 1993;**13**:548–54

124. Watts GF, Mazurkiewicz JC, Tonge K, *et al*. Lipoprotein (a) as a determinant of the severity of angiographically defined carotid atherosclerosis. *Q J Med* 1995;**88**:321–6.

125. Delanty N, Vaughan C. Vascular effects of statins in stroke. *Stroke* 1997;**28**:2315–20.

LIPOPROTEIN(a) LEVELS IN YOUNG ISCHEMIC STROKE

Name	**Age**	**Sex**
Occupation	**IP NO**	
Address	**D.O.A** **D.O.D**	

Diagnosis

Presenting complaints

Past history HT ☐ DM ☐ CAD ☐ TIA ☐
☐ Valvular Heart Disease
☐ Renal disease ☐ Malignancy ☐ Rheumatoid Arthritis
☐ Hyperlipidemia

Personal history Smoker ☐ Alcohol ☐

Physical examination BP
PR Weight Height
BMI
Carotids
Vessel wall thickening
CNS findings

Investigations

Hb gm% TC DC PCV ESR
Urine Albumin Sugar Deposits
Blood sugar Blood Urea Serum Creatinine
ECG
Serum Lipoprotein(a) mg/dl
HIV **VDRL**
CT findings

Outcome

The prevalence rates of stroke from various major epidemiological studies in India

Table A

Zone	Place	Rural / Urban	Year	Population	Crude Prevalence rate per 100,000	Age Adjusted Rate Per 100,000
North	Rohtak, Haryana,	Urban	1971-74	79,046	44	-
	Kuthar valley, Kashmir,	Rural	1986	63,645	143	244*
West	Mumbai, among the Parsis	Urban	1985	14,010	842	424*
	Mumbai	Urban	1997	145,456	220	-
East	Malda, West Bengal	Rural	1989-90	37,286	126	-
	Baruipur, West Bengal	Rural	1992-93	20,842	147	-
	Kolkata	Urban	1998-99	50,291	147	334**
South	Vellore	Rural	1969-71	258,576	57	84
	Gowribidinur, Karnataka	Rural	1982-84	57,660	52	-
	Bangalore	Rural	1993-95	51,055	165	262
	Bangalore	Rural	1993-95	51,502	136	-

***Age standardized to 1960 US population; ** Age standardized to 1996 US population; Year of US population for age-standardization not known**

The Annual Incidence Rates of stroke from various epidemiological studies in India

Table B

Place	Rural / urban	Year	Population	Annual incidence rate per 100,000	Age adjusted annual incidence rate per 100,000
Vellore	Rural	1969-71	258,576	13	-
Kolkata	Urban	1998-99	50,291	36	105*
Baruipur, West - Bengal	Rural	1993-98	20,842	124	262**

***Age adjusted to 1996 US Population; **Age-adjusted to 1990 US Population**

S.NO	Name Ip.No	Age	Sex	Complaints	HT	DM	Smoker	Alcoholism	Family h/o stroke	Recurrent stroke	BMI	PR	BP in mmHg	CVS	RBS mg/dl	ECG	LP(a) mg/dl	CT BRAIN	DIAGNOSIS	OUTCOME
1	Mr. Neelakandan 904661	23	M	Weakness Lft. UL+LL	No	No	No	No	Yes	Yes, same side	21.55	74	130/80	$S_1 S_2$ +	70	Normal	109	Rt Frontoparietal infarct	CVA / Rt. Hemispherical stroke	Discharged
2	Mr. Packirisamy 912423	40	M	Weakness Rt. UL+LL aphasia	No	No	Yes 5/day	Yes 1/week	No	No	22.33	68	124/86	$S_1 S_2$ +	82	Normal	< 10.00	Lft.MCA Infarct	CVA/ Lft.hemispherical stroke	Discharged
3	Mr. Arumugam 906218	40	M	Weakness Rt. UL+LL	No	No	Yes 10/day	No	No	No	23.83	78	110/80	$S_1 S_2$ +	86	Normal	55.10	Lft.MCA infarct; no mass effect	CVA / Lft. Hemispherical stroke	Discharged
4	Miss. Rassiya 912678	19	F	Weakness Rt. UL+LL	No	No	No	No	No	No	20.13	80	116/84	$S_1 S_2$+	84	Normal	< 10.00	Lft. Cortical infarct	CVA / Lft. Hemispherical stroke	Discharged
5	Mr. Muruganandham 926378	27	M	Weakness Lft. UL+LL	No	No	Yes 4/day	No	No	No	25.6	78	126/80	$S_1 S_2$ +	94	Normal	37.40	Rt. Temporal basal ganglia and paraventricular region infarct	CVA / Rt. Hemispherical stroke	Discharged
6	Mr. Ram 945127	33	M	Weakness Lft. UL+LL	No	No	Yes 8/day	Yes 2/week	No	No	23.01	68	110/86	$S_1 S_2$+	92	Normal	< 10.00	Rt. Internal capsule region infarct	CVA / Rt. Hemispherical stroke	Dischargedd
7	Miss. Umarani 940978	22	F	Weakness Rt. UL+LL	No	No	No	No	No	No	19.72	82	110/80	$S_1 S_2$ +	88	Normal	< 10.00	Lft. Parieto temporal infarct	CVA / Lft. Hemispherical Ischemic stroke	Discharged
8	Mr. Sekar 919767	30	M	Weakness Rt. UL+LL	No	No	No	No	No	No	26.56	70	116/78	$S_1 S_2$ +	98	Normal	62.20	Normal study No evidence of hemorraghe	CVA / Lacunar infarct	Discharged
9	Mr. Sekar 944396	38	M	Weakness Lft. UL+LL	No	No	Yes 5/day	Once/a week	No	No	25.50	82	138/74	$S_1 S_2$+	118	Normal	47.90	Hypodensity in the region of internal capsule Rt. Side	CVA / Rt. Hemispherical stroke	Discharged
10	Mr. Sekar 934643	37	M	Weakness Lft. UL+LL	No	No	No	2 drinks/ week	No	No	25.00	90	118/68	$S_1 S_2$+	100	Normal	40.20	Hypodensity in the region of Rt. Internal capsule	CVA / ischemic Rt. Hemispherical stroke	Discharged
11	Mr. Murugesan 945611	37	M	Weakness Lft. UL+LL	No	No	No	No	No	No	25.63	88	134/70	$S_1 S_2$+	98	Normal	30.90	Rt. MCA infarct	CVA / Rt. Hemispherical Ischemic stroke	Discharged
12	Mr. Arputharaj 947816	34	M	Weakness Rt. UL+LL	No	No	8 Beedi / day	No	No	No	21.63	74	110/80	$S_1 S_2$+	88	Normal	52.70	Lft. MCA infarct	Lft. Hemispherical stroke	Discharged
13	Mr. Vadivel 947816	40	M	Weakness Rt. UL+LL	No	No	No	No	No	Yes, same side	20.76	86	124/80	$S_1 S_2$+	74	Normal	108.00	Lft. Internal capsular & basal ganglia infarction	Lft. Hemispherical stroke	Discharged
14	Mr. Senthil Kumar 950149	35	M	Weakness Lft. UL+LL	No	No	No	No	No	No	27.71	80	110/80	$S_1 S_2$+	114	Normal	46	Rt. MCA infarct	Rt. Hemispherical stroke	Dischargedd
15	Mr. Vengadesan 953882	30	M	Weakness Lft. UL+LL	No	No	No	No	No	No	23.52	78	130/80	$S_1 S_2$+	110	Normal	55	Rt. Parieto occipital infarct	Rt. Hemispherical stroke	Discharged
16	Mr. Ravi 953631	35	M	Weakness Rt. UL+LL	No	No	No	No	No	No	21.40	72	124/86	$S_1 S_2$+	128	Normal	40.0	Lft. Watershed infarct	Lft. Hemispherical stroke	Discharged
17	Mr. Jeyaseelan 955860	30	M	Weakness Rt. UL+LL	No	No	No	No	No	No	22.14	80	130/80	$S_1 S_2$+	110	Normal	< 10.00	Lft. Internal capsular infarct	Lft. Hemispherical stroke	Discharged
18	Mr. Palaiya 956966	30	M	Weakness Rt. UL+LL	No	No	No	No	No	No	19.53	64/mt	120/80	$S_1 S_2$+ head	126	Normal	62.00	Lft. MCA territory infarct	Lft. Hemispherical stroke	Discharged
19	Mr. Chandrasekhar 957361	18	M	Weakness Rt. UL+LL	No	No	No	No	No	No	34.39	74	130/82	$S_1 S_2$ +	70	Normal	36.00	Lft. MCA infarct	Lft. Hemispherical stroke	At request Discharged

20	Mr. Sundaramoorthy 957472	40	M	Weakness Rt. UL+LL	No	No	5 cigar/day	NO	NO	Yes, same side	34.37	82	130/86	$S_1 S_{2+}$	111	Normal	48.00	Lft. Internal capsular infarct	CVA / Lft. Hemispherical Ischemic stroke	Discharged
21	Mr. Boominathan 936180	35	M	Weakness Lft. UL+LL	No	No	5cigarette /day	NO	NO	NO	28.60	86	130/86	$S_1 S_2$ +	98	Normal	38.60	Rt. MCA territory infarct	CVA / Rt. Hemispherical Ischemic Stroke	Discharged
22	Mr. Karunanidhi 961735	35	M	Weakness Rt. UL+LL of aphasia	No	No	5cigarette /day 10 years	NO	NO	NO	25.28	84	110/80	$S_1 S_{2+}$	91	Normal	55.00	Lft. MCA infarct	CVA / Lft. Hemispherical Ischemic stroke	Discharged
23	Mr. Kuzhandaisamy 935642	40	M	Weakness Rt. UL+LL	No	No	NO	NO	NO	Yes, same side	23.10	88	120/84	$S_1 S_{2+}$	100	Normal	48.30	Lft. MCA infarct Old Lft. Frontal infarct	CVA / Lft. Hemispherical & current stroke	Discharged
24	Mr. Paneerselvam 927145	40	M	Weakness Lft. UL+LL	No	No	NO	NO	NO	NO	26.56	84	130/86	$S_1 S_{2+}$	86	Normal	62.10	Rt. MCA infarct	CVA / Rt. Hemispherical Ischemic Stroke	Discharged
25	Mr. Anbazhagan 937652	37	M	Weakness Rt. UL+LL	No	No	1pack /day 5 years	NO	NO	NO	25.00	84	110/86	$S_1 S_{2+}$	114	Normal	46.00	Lft. Internal capsular infarct	CVA / Lft. Hemispherical Ischemic stroke	Dischargedd
26	Mr.Prabhakar 957214	29	M	Abd pain loose stools	No	No	No	No	No	No	20.06	88	120/80	$S_1 S_{2+}$	110	Normal	24.12	No	Gastroenteritis	Discharged after 6 days
27	Mr.Satish 957190	21	M	Fever x 2 days	No	No	No	No	No	No	26.98	90	110/80	$S_1 S_2$	126	Normal	12.80	No	Viral fever	Discharged after 7 days
28	Mr.Azhagapa Devar 955996	34	M	Weakness of all four limbs	No	No	No	No	No	No	30.04	78	130/80	$S_1 S_{2+}$	114	Normal	<10	No	Hypokalemic periodic paralysis	Discharged after 2 days
29	Mrs.Devi 965072	23	F	Viral fever	No	No	No	No	No	No	29.05	80	114/80	$S_1 S_{2+}$	90	Normal	22	No	Viral fever	Discharged after 2 days
30	Mr. Ganesan 955926	31	M	Seizures	No	No	No	No	No	No	30.22	78	110/80	$S_1 S_{2+}$	86	Normal	19	No	Seizure disorder	Discharged after 2 days
31	Mr.Prabhakaran 947510	16	M	Viral fever	No	No	No	No	No	No	25.56	74	100/70	$S_1 S_{2+}$	78	Normal	18.4	No	Viral fever	Discharged after 5 days
32	Mr. Ravi 947446	40	M	Weakness of all four limbs	No	No	No	No	No	No	27.16	88	110/80	$S_1 S_{2+}$	96	Normal	21	No	Hypokalemic periodic paralysis	Discharged after 2 days
33	Miss.Sandhya 960075	16	F	Increased fatiguability	No	No	No	No	No	No	26.02	78	110/80	$S_1 S_{2+}$	88	Normal	<10	No	Nutritional anaemia	Discharged after 4 days
34	Mr. Jamal Mohammed 926926	27	M	100ml of hemetemein	No	No	10 cig/ day	2-3 times/week	No	No	27.68	86	110/86	$S_1 S_{2+}$	100	Normal	18.74	No	Minor UGI bleed	Discharged after 3 days
35	Mr. Shanmugavel 927835	27	M	Consumption of rat killer power	No	No	No	No	No	No	28.30	94	110/80	$S_1 S_{2+}$	118	Normal	63	No	Rat killer poisoning	Discharged after 3 days
36	Mr. Rameshkumar 929164	29	M	Increased fatigability	No	No	15cig/day	No	No	No	18.93	78	110/80	$S_1 S_{2+}$	126	Normal	27	No	Nutritional anemia	Discharged after 6 days
37	Mr.Ramachandran 923004	27	M	Fever 1 week	No	No	5cig/day	No	No	No	21.48	88	116/70	$S_1 S_{2+}$	108	Normal	21.6	No	Viral fever	Discharged after 2 days
38	Mr. Ramasamy 923039	31	M	Chest pain	No	No	10cig/day	2-3 drink/ week	No	No	24.2	78	120/84	$S_1 S_{2+}$	98	Normal	10.8	No	Non cardiac chest pain	Discharged after 1 days
39	Mr. Chandrasekhar 926011	32	M	Consumption of unknown poisoning	No	No	20cig/day	4-5 drink/ week	No	No	18.62	74	116/80	$S_1 S_{2+}$	104	Normal	24.9	No	Unknown poisoning	Discharged after 3 days

40	Mr. Mohan 958999	36	M	One episode of seizure	No	No	12cig/day	No	No	No	21.77	74	114/80	$S_1 S_{2+}$	104	Normal	57.0	No	Seizure disorder	Discharged after 5 days
41	Mr.Illavarasan 959059	37	M	Unknown bite	No	No	No	No	No	No	29.00	82	116/70	$S_1 S_{2+}$	98	Normal	18.2	No	Unknown bite	Discharged after 2 days
42	Mr. Ponnusamy 960995	37	M	Snake bite	No	No	6cig/day	No	No	No	24.22	84	128/80	$S_1 S_{2+}$	110	Normal	25.2	No	Non poisonous snake bite	Discharged after 3 days
43	Mr. Rajkumar 959892	38	M	Snake bite	No	No	3cig/day	No	No	No	23.52	90	118/80	$S_1 S_{2+}$	94	Normal	26.1	No	Non poisonous snake bite	Discharged after 4 days
44	Mr. Michael 959803	40	M	Fever 4 days	No	No	5 cig/day	No	No	No	20.67	92	110/80	$S_1 S_{2+}$	120	Normal	19.9	No	Viral fever	Discharged after 4 days
45	Mr. Siva 956300	36	M	Epigastric pain*2days	No	No	20 cig/day	Consumes 5 drink/week	No	No	21.67	98	116/84	$S_1 S_{2+}$	116	Normal	<10	No	Gastritis	Discharged after 2 days
46	Mr.Murugan 961380	37	M	Fever 1 week	No	No	No	No	No	No	28.44	106	120/80	$S_1 S_{2+}$	118	Normal	21.8	No	Viral fever	Discharged after 4 days
47	Mr.Pandiyan 960275	36	M	Unknown bite	No	No	No	No	No	No	22.49	104	118/76	$S_1 S_{2+}$	120	Normal	50.6	No	Unknown bite	Discharged after 2 days
48	Mr.Sivaraman 959327	38	M	Fever breath Lessness	No	No	No	No	No	No	26.56	94	110/80	$S_1 S_{2+}$	120	Normal	12	No	Rt lower lobe pneumonia	Discharged after 6 days
49	Mr.Muthuvel 959325	35	M	Cough with expectoration	No	No	10cig/day	No	No	No	21.26	110	114/82	$S_1 S_{2+}$	114	Normal	20.3	No	Pulmonary tuberculosis	Discharged after 4 days
50	Mr.Dhanapal 958940	35	M	Unknown bite	No	No	No	No	No	No	21.25	88	120/80	$S_1 S_{2+}$	96	Normal	25	No	Unknown bite	Discharged after 4 days